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ANNUAL REPORT
OF
PROGRAM ACTIVITIES
NATIONAL CANCER INSTITUTE
Fiscal Year 1980
Part V

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service National Institutes of Health

ANNUAL REPORT

OF

PROGRAM ACTIVITIES

NATIONAL CANCER INSTITUTE

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Part V

Division of Cancer Research Resources and Centers

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NATIONAL CANCER INSTITUTE

DIVISION OF CANCER RESEARCH RESOURCES AND CENTERS

ANNUAL REPORT

October 1, 1979 through September 30, 1980

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FOREWORD BY THE DIRECTOR

The Division of Cancer Research Resources and Centers, one of the five major components of the National Cancer Institute, plans and administers grant programs for the support of cancer research and training in both the United States and foreign countries throughout the World. In line with the objectives of the National Cancer Institute reorganization in 1979, which were to separate program from peer review, selected programs and their supporting staff were transferred from the DCRRC to the Divisions having major responsibility for their program's activities. Programs transferred to the Division of Cancer Biology and Diagnosis were Immunology and Tumor Biology; to the Division of Cancer Cause and Prevention went the programs in Carcinogenesis, Epidemiology, and Viral Oncology; Drug Development and Pharmacology, Radiation, and Clinical Oncology went to the Division of Cancer Treatment; and responsibility for the Centers Program was assumed by the Office of the Director, NCI.

The activities of the Division are now largely devoted to the review, analysis, and management of the grant programs involving both basic and clinical research, as well as the training and education activities. In addition to the review and administration of grants, the Division has also assumed responsibility for the review of research contracts.

At present the Division is composed of the Grants Administration Branch, Grants Financial Branch, Research Analysis and Evaluation Branch, Grants Review Branch, and Contracts Review Branch. The Research Facilities Branch, Organ Sites Branch, Clinical Manpower Branch, and Research Manpower Branch were transferred to other Divisions late in this fiscal year; therefore, reports on their activities are included in this Division's report.

National Cancer Advisory Board

The Director of the Division of Cancer Research Resources and Centers also serves as the Executive Secretary of the National Cancer Advisory Board. The Board has the responsibility for the second phase of the dual review process and also advises the Director of the National Cancer Institute and Director, NIH, on policy matters regarding cancer grant and contract-supported research and training programs. A new subcommittee of the Board has been formed, the Subcommittee on Board Activities and Agenda, which has taken an active role this past year in reviewing the activities and manner of operation of the Board and in planning the Board agendas to provide the most efficient means of review for all the activities and programs of the Institute, as well as reviewing the extramural research supported by grants.

An orientation handbook has been prepared for the use of the NCAB which includes the history of the NIH and NCI, and instruction on the methods of the peer review process employed by the Department of Health and Human Services and the National Institutes of Health.

Committee Management

The DCRRC has responsibility for the committee management activities of the NCI which involves the nomination, clearance, invitation, appointment, and management of the NCI review and advisory committees. During fiscal year 1980 NCI had 26 chartered committees with approximately 425 members. These committees of consultants are divided into two broad categories--scientific review groups and program advisory groups. The primary function of the scientific review groups is to determine the scientific merit of research grant applications and contract proposals. The program advisory groups provide the broad perspective on the research needs and scientific opportunities of the Institute and their social impact.

Liaison with NIH Committees

The Director of the DCRRC is the NCI representative on the following NIH Committees: the Extramural Program Management Committee (EPMC), the Review Policy Committee (RPC), and the Research Resources Coordinating Committee (RRCC). He keeps the Director of NCI, the Division Directors, and other staff advised on policies and procedures for the extramural programs, and helps formulate policies and procedures for the operation of the grants and contracts programs.

Personnel Changes

There were several personnel changes in the Office of the Director, DCRRC, during this past year. The Director, Dr. Thomas J. King, left the NCI July 31 to become the Director of the Joseph and Rose Kennedy Institute of Ethics, Georgetown University.

Another major loss to the Division came with the retirement of Dr. Samuel Price, Acting Assistant Director, who retired May 30 and joined the staff of the University of Maryland as University Coordinator for Sponsored Research. The Division's Administrative Officer, Mrs. Edith Phillips, also retired and Mrs. Jean Stein has replaced her as AO.

Budget

The NCI fiscal year 1980 grants budget was $514.7 million as compared to $474.7 million in fiscal year 1979. This permitted funding in fiscal year 1980 of 33 percent of competing Traditional (R01) grants through priority score 215. At the fiscal year 1979 budget level, however, it was possible to pay 44 percent of competing Traditional grants with a priority score cut-off of 240.

OFFICE OF THE SPECIAL ASSISTANT FOR SPECIAL PROJECTS

The Office of the Special Assistant for Special Projects is primarily concerned with coordinating functions. Principal activities were in the following areas: (a) National Cancer Advisory Board; (b) Conference Program supported both by R-13 grants and Fogarty International Center (FIC) contracts; (c) Cancer Research Emphasis Grants (CREG), and later, Request for Applications (RFA) and Program Announcements; (d) DNA recombinant research; and (e) Freedom of Information (FOI) and Privacy Act (PA). Each of these activities will be addressed in turn.

National Cancer Advisory Board

Activities concerned with the NCAB include not only the routine planning of pre and post-Board meetings, but more importantly, advising staff of all Divisions regarding policy and procedures and serving as Executive Secretary of the Special Actions Subcommittee. An interesting activity of the Subcommittee this year was an in-depth review of several grant programs in the Division of Cancer Treatment, including Biochemistry and Pharmacology; Radiation Biology and Therapy; and Clinical Oncology. In addition, the subcommittee began a review of P01 grants; and of instances when there was disagreement between an initial review group and a site visit team.

Conference Program

The bulk of extramural conference support is through R-13 grants or Fogarty International Center (FIC) contracts. In general, an R-13 grant is appropriate if the subject of the conference is of prime relevance to one Institute; the FIC contract if the subject is of interest to several B/I/D's. R-13 grants undergo outside peer review conducted through this office and are administered by NCI Programs. FIC contracts are reviewed by NCI personnel with recommendations made back to the conference coordinator but are administered by the FIC. The following tables summarize the year's activity.

Table 1

FOGARTY CONFERENCES - FY 80 *

SCIENTIFIC AREA	NUMBER REVIEWED	NUMBER PAID	AMOUNT PAID
Tumor Biology	28	18	$ 49,250
Viral Oncology	4	3	15,000
Carcinogenesis	3	1	7,500
Immunology	12	12	91,750
Drug Development	1	1	2,000
Multidisciplinary	29	9	29,000
Total:	77	44	$ 194,500

* Figure based on approximately nine-month period from October '79 to June '80.

Table 2

NCI R-13 Grants - FY 80 *

	Number	Direct Cost
Reviewed:	34 **	$1,696,196
Approved: mean priority score - 215	31	1,500,754
awarded: mean priority score - 165	20	903,130
not awarded: mean priority score - 314	11	-
Disapproved:	3	-

* Represents 9-month period from October '79 to June '80.
** Including three type 5's.

Table 3

Cancer Activity R-13 Grants - FY 80 *

	Reviewed		Paid	
	Number	Direct Cost	Number	Direct Cost
Diagnostic Radiology	1	$21,000	-	-
Nutrition	1	175,796	-	-
Tumor Biology	5	246,889	4	$141,023
Immunology	3	146,112	1	32,688
Epidemiology	4	355,855	3	274,709
Breast Cancer	2	48,175	1	15,000
Biological Carcinogenesis	4	172,931	4	164,866
Carcinogenesis	6	112,089	2	34,300
Cancer Control	1	30,280	-	-
Clinical Oncology	5	132,477	3	72,172
Biochemistry and Pharmacology	1	13,466	1	13,466
Other **	1	241,126	1	154,906
Total	34	$1,696,196	20	$903,130

* Represents 9-month period from October '79 to June '80
** UICC International Cancer Conference

Table 4

Funded R-13 Conferences by Titles

Conferences for Personnel of Cancer Data Programs Date: April 23-25, 1980	P.I.: Zippin,Calvin, Sc.D. Location: Albany, NY
13th Jerusalem Symposium on Carcinogenesis Date: April 28 to May 2, 1980	P.I.: Ts'O, Paul O., Ph.D. Location: Jerusalem, Israel
Meeting on Mammary Cancer in Experimental Animals and Man Date: May 11 to May 14, 1980	P.I.: Hageman, P., Sc.D., Location: Netherlands Cancer Inst.
International Workshop in Oncogenic Viruses Date: May 26-June 6, 1980	P.I.: Kraiselburd, Edmundo, Ph.D. Location: Univ. of Puerto Rico, San Juan, PR
The Second World Conference on Lung Cancer Date: June 9-13, 1980	P.I.: Higgins, George A. Jr., M.D. Location: Malmo, Sweden
International Symposium on Human Testicular Cancer Date: June 26-28, 1980	P.I.: Fraley, Elwin E., M.D. Location: Univ. of Minnesota, MN
Support for Cancer Research Center Courses Date: Summer, 1980	P.I.: Watson, James D., Ph.D. Location: Cold Spring Harbor Lab. NY
Supplement for Support for Cancer Res. Center Courses Date: Summer, 1980	P.I.: Watson, James D., Ph.D. Location: Cold Spring Harbor Lab. NY
1980 Annual Symposium on Fundamental Cancer Research Date: Summer, 1980	P.I.: LeMaistre, Charles A., M.D. Location: Univ. of Texas Cancer Center
Gordon Conference on Mutagenesis and Carcinogenesis Date: July 14-18, 1980	P.I.: Strauss, Bernard S., Ph.D. Location: Kingston, RI
Chemotherapy of Clinical and Experimental Cancer Date: July 28-August 1, 1980	P.I.: Parks, Robert E. Jr., Ph.D. Location: Plymouth State College, NH

International Forum: Cancer Cell Organelles Date: August 12-15, 1980	P.I.: Morre, James D., Ph.D. Location: Surrey, England
Gordon Research Conference on Cancer 1980 Date: August 17-22, 1980	P.I.: Becker, Frederick F., M.D. Location: New London, NH
Mechanisms in Human Cancer Immunology Symposium Date: October, 1980	P.I.: Saunders J. Palmer, Ph.D. Location: Univ. of Texas, Galveston, TX
Clinical Conference Gastrointestinal Cancer Date: November 5-8, 1980	P.I.: Blumenschein, George R., M.D. Location: Univ. of Texas Cancer Center
Seminars and Workshops in Techniques of Cancer Research Date: Series, 1980	P.I.: King, Donald W., M.D. Location: Univ. of Colorado, Denver, CO
Support for Symposia on Quantitative Biology Date: 1980 Series	P.I.: Watson, James D., Ph.D. Location: Cold Spring Harbor, NY
Program of the International Union Against Cancer Date: 1980-1984 Series	P.I.: Delafresnaye, John F., M.D. Location: Rue Du Conseil General, Geneva, Switzerland
Epidemiology and Cancer Registries in the Pacific Basin Date: Fall, 1981	P.I.: Henderson, Brian G., M.D. Location: Maui, HA
International Cancer Congress (UICC) Date: Fall, 1982	P.I.: Mirand, Edwin A., Ph.D. Location: Cancer Center, Seattle, WA

Cancer Research Emphasis Grants, Requests for Applications, and Program Announcements

During the past year the CREG program was supplanted by the use of Request for Applications (RFA) and Program Announcements (PA). No further additions will be made to the CREG program, and when the present grants have run out, this program will not exist. In the meantime, various NCI Divisions have announced their new programs by publication of the RFA or PA in the NIH Guide to Grants and Contracts. This office advises, clears and approves these documents for submission to the NIH publication. Publications for fiscal year 1980:

"Studies of Immunocompetent Cells Infiltrating Human Breast Cancer." NCI-DCBD-BCPCB-80-1. February 22, 1980.

An attempt to stimulate research of the immunologic activity within the breast cancer tumor, specifically identification of cell types and their reactivity in relation to diagnosis and prognosis.

"Training Program in Veterinary Pathology and Comparative Pathology." NIH-NCI-DCRRC -RMB 80-2. January 25, 1980, Volume 9, number 2, page 41.

The goal of this RFA is to double the annual production of board-certifiable veterinary pathologists within five years, and to increase the national pool of comparative pathologists. There is an especially urgent need for cancer research scientists trained in this field.

"Exploratory Grants for Cancer Control at Comprehensive Cancer Centers." NIH-NCI-DCCR-CSPB-80-3. February 22, 1980.

The goal of this RFA is to provide a grant support mechanism which the Comprehensive Cancer Center may use to explore, strengthen, and develop its long-range cancer control activities and portions of its training, education, and dissemination activities.

"Correlation Between Microscopic Characteristics of Primary Breast Tumors and Subsequent Patient Survival." NCI-DCBD-BCPCB-80-5. June 6, 1980.

A number of studies have been done on gross and histological parameters in breast cancer that have been suggested for use

in predicting prognosis or estimating survival. However, none of these has proved to be an absolute or fully objective predictor. This RFA, then, is seeking studies delineating other parameters that might better correlate with, or be used to predict prognosis and survival. It calls for a retrospective study based on known survival, but using tissue samples taken at the time of original surgery to search for parameters that correlate with survival.

Program Announcements:

"Interspecies Comparisons in Carcinogenesis." NIH-NCI-DCCP-CPC-80-6

The proposed RFA encompasses both basic and applied studies intended to provide insights and approaches to an understanding of similarities and differences between experimental animals and humans with emphasis on the use of accessible human cells, tissues, body fluids, and excreta, and on studies which focus on quantitative relationships relative to the carcinogenesis process.

"Preventive Oncology Academic Awards." DCCP. January 3, 1979.

This program is to stimulate research and education for cancer prevention in schools that do not have such programs and to strengthen and improve these programs in schools that do. It is an effort to develop superior faculty to ensure superior learning opportunities as well as to facilitate interchange of ideas and methods among awards and institutions.

"Smoking, Cancer and Health Program." DCCR. January 3, 1979.

The NCI's Smoking, Cancer and Health Program desires to expand its involvement with the role of smoking as a public health problem in cancer cause and prevention. The program is seeking applications for research and demonstration grants concerned with basic and applied studies in toxicology, epidemiology, prevention behavior, attitudes, pharmacology, education, information, training, and other appropriate areas related to Smoking and Health.

"Diet, Nutrition and Cancer Program Announcement of Research Interests in Alcohol and Cancer." DCCR - January 3, 1979.

Alcohol combined with tobacco smoking is an established risk factor for cancers of the oropharynx, esophagus, and larynx. It should be possible to clarify further the role of alcohol itself, the modifying effects of tobacco, close-response relationships, and nutritional co-factors.

"Research Related to Genetic Susceptibility to Human Breast Cancer." - Breast Cancer Program. DCBD. January 21 1980.

Recent studies have indicated that in some families breast cancer appears to be segregating as a Mendelian trait, suggesting that one or more human genes are responsible for the susceptibility. Some areas of investigation to be developed in this area may be:

(1) Which, if any, environmental or cultural risk factors interact with genetic susceptibility and how these factors are expressed at physiological and biochemical levels.
(2) What proportion of human breast cancers may be accounted for or strongly influenced by gene susceptibility; how many forms exist and how common is each of these forms.
(3) Comparison of natural history of genetically influenced versus non-familial breast cancer.

"Experimental Research Related to Mammographic Screening for Human Breast Cancer." DCBD. January 21, 1980.

This program announcement seeks responses with a special emphasis toward developing our understanding of the basic principles of radiation carcinogenesis and cocarcinogenesis to supply quantitative predictions for the number of human cancers expected to be induced by radiation.

"Cancer Clinical Treatment Research." DCT. February 22, 1980.

The program is seeking responses for research grants concerned with the clinical treatment of cancer. Those of particular interest include the elucidation of the effects of various treatments and related tissue responses, toxicology and the importance of host factors in disease occurence, rate of progression, and curability. Improved experimental design, data management, and statistical analysis, as well as specific experimental developments in supportive care methods and modalities, are integral aspects of this program. Applications dealing with innovative approaches in surgical oncology are of particular interest.

CREG PROGRAM *
FY 80

DIVISION	RFA#	#GRANTS	RECOMMENDED OR AWARDED DIRECT COSTS	TOTAL COSTS
DCT	01	1	$ 15,000	$ 21,750
	03	8	1,013,079	1,372,727
	04	10	941,910	1,372,727
	05	4	215,766	298,754
	06	3	242,079	347,904
	07	11	720,208	938,003
DCCP	01	4	212,739	294,534
	02	2	188,648	263,163
	03	3	184,399	257,539
	04	1	65,745	92,043
	10	1	105,070	123,788
	17	4	350,498	384,416
	18	4	162,466	225,710
	19	2	69,925	87,012
	22	1	136,403	164,265
	30	2	46,668	80,640
	32	1	48,000	48,000
	33	1	130,445	182,623
	18	63	$4,849,048	$ 6,766,146

(*Includes Grants awarded and those to be Awarded)

DNA Recombinant Research

The office is responsible for disseminating policy information and for assuring that all NCI grants of which DNA recombinant research is a part are cleared by the NIH Office of Recombinant DNA Activities.

A summary of activities in fiscal year 1980 is as follows:

PROGRAM AREA	NUMBER OF PROJECTS	DIRECT COSTS *
Biol. Carcinogenesis	62	$ 13, 622,447
Tumor Biology	35	7,308,093
Multidisciplinary	16	23,376,066
Chem. & Phys. Carc.	7	975,321
Immunology	5	1,406,901
Creg DCCP	3	210,596
Biochem. & Pharmacology	2	257,268
Cancer Control	1	136,693
	131	$ 47,293,385

* This does not represent the amount spent on DNA recombinant research; it is the total amount for a grant in which DNA research may be a major or minor fraction.

Freedom of Information and Privacy Acts

This office serves as a coordinating point and in an advisory capacity for FOI and PA requests pertaining to NCI grants. Privacy Act requests pertaining to a single program are routinely routed from this office to a Program Director; and the office advises and coordinates the response to the more complicated Freedom of Information requests.

The following table reflects the volume of requests answered.

PUBLIC INFORMATION REQUESTS

Calendar Year 1979 *	
PA	1805
FOI	35
Calendar Year 1980 *	
PA	1610 **
FOI	38 **

* NIH reports Freedom of Information Act and Privacy Act requests by calendar year, not fiscal year.

** Estimated, based on actual number for January 1 - June 30, 1980.

NATIONAL ORGAN SITE PROGRAMS BRANCH

The National Organ Site Programs consist of grant-supported National Projects of targeted cancer research. Each Project is a planned research effort oriented toward cancer at a specific organ site. Currently there are National Organ Site Projects concerned with cancers of the urinary bladder, large bowel, pancreas, and prostate. The planning, direction, and coordination of each Project are provided at a headquarters institution other than the NCI. A national project director, who is not an employee of NCI, is assisted in planning and administration by a headquarters staff and by a working cadre of active research scientists recruited from institutions throughout the Nation. Grant applications are received by the headquarters and are reviewed by the working cadre and by the National Cancer Advisory Board. Applications which are judged scientifically meritorious and relevant to the aims of the Project are recommended to the NCI for funding.

Each national project director is a recognized clinical or laboratory scientist with a strong interest in, and professional identification with, a specific organ site cancer. The National Bladder Cancer Project is under the direction of Dr. Gilbert H. Friedell, St. Vincent Hospital, Worcester, Massachusetts; the National Large Bowel Cancer Project, Dr. Murray M. Copeland, M. D. Anderson Hospital and Tumor Institute, Houston, Texas; the National Pancreatic Cancer Project, Dr. Isidore Cohn, Jr., Louisiana State University School of Medicine, New Orleans, Louisiana; and the National Prostatic Cancer Project, Dr. Gerald P. Murphy, Roswell Park Memorial Institute, Buffalo, New York.

NATIONAL BLADDER CANCER PROJECT

Description

The primary goal of the National Bladder Cancer Project (NBCP) is to sponsor and encourage laboratory and clinical research directed toward improving the techniques available for managing, controlling, or preventing cancer of the urinary bladder. The Project was initiated eight years ago following a year of planning by many of the investigators then active in this field of research. The Project was competitively reviewed by a Special Review Committee from the NCI on October 22-24, 1979, and was awarded an additional five years of support beginning May 1, 1980.

Over these eight years, a multidisciplinary research program has been developed to encourage collaboration and exchange of informantion between clinical and laboratory scientists engaged in studies related to bladder cancer. Studies are supported which seek to identify carcinogenic factors and develop methods for minimizing or eliminating their effect, improve detection methods and identify new high-risk populations, increase understanding of the pathogenesis and carcinogenesis processes and find methods for interfering with these processes, develop improved methods of diagnosis in order to identify those patients most suitable for a specific available treatment regimen, and find better methods for treating the disease.

The Project consists of investigator-initiated grants. Qualified investigators are encouraged to submit grant applications outlining approaches which they feel are most likely to accomplish specific objectives within the overall guidelines of the project. In addition to assessment of scientific merit, all grant applications submitted to the NBCP are evaluated for relevance to the program needs and as to whether or not the work proposed is significant to the achievement of the NBCP goals.

A collaborative effort is supported by the NBCP for prospective studies of patients with bladder carcinoma--the National Bladder Cancer Collaborative Group A (NBCCGA). The organization of the NBCCGA is based upon the concept that bladder cancer is a progressive disease and that increased understanding of the progression for various subgroups of patients under treatment will contribute to improved therapy through improved diagnosis and the classification of patients. Consequently, a basic protocol of this Group is the surveillance of all patients with bladder cancer admitted by participating physicians. When the most suitable treatment selection is not known, randomized clinical trials are established to provide the data from which such a decision can be derived. Collaborative Group A at present consists of twelve institutions: Massachusetts General Hospital, University of Tennessee, Virginia Mason Research Center, Rush-Presbyterian-St. Luke's Medical Center, Unviversity of Oregon, Medical College of Virginia, Roswell Park Memorial Institute, University of Iowa, University of California at San Diego, Johns Hopkins University, St. Vincent Hospital (Pathology Laboratory), and Georgetown University (Statistical Center).

Accomplishments

A special issue focusing on "Urinary Bladder Cancer," was published in Seminars in Oncology, Volume IV, Number 2, June, 1979. An introduction by the Project Director and the Headquarters Staff and 18 articles from participants in the NBCP describe the current status of various aspects of this disease organized in the following categories: understanding the disease; assessing the disease and the host; therapeutic approaches based on disease assessment; and research probes and planning techniques. The last comprehensive assessment by those engaged in the Project was in the proceedings of the previous National Bladder Cancer Conference published in August 1977 in Cancer Research, Volume 37. Number 8, Part 2, Pages 2743-2973.

During the past year, data from experiments on the promotional aspects of carcinogenesis have led to an increased understanding of bladder carcinogenesis and a new appreciation of the complexity of this process (Cohen, 1979). It has been shown in rats that when sodium saccharin or DL-tryptophan are fed as promoters following six weeks of 0.2% FANFT, a high proportion of test animals develop bladder tumors. The tumors which develop following feeding of saccharin occurred earlier and were more invasive. No tumors were found following the feeding of saccharin or DL-tryptophan alone and few tumors were found following six weeks of FANFT feeding. The experiment has been repeated using four weeks of 0.2% FANFT followed by either sodium saccharin or L-tryptophan. No tumors were found in rats fed FANFT, saccharin, or tryptophan alone; but tumors appeared in groups of rats fed FANFT plus either of the other two chemicals, confirming the previous findings.

The role of sodium saccharin in human bladder cancer is less clear. Contrary to the reports of others, the data from the International Case-Control Study of Bladder Cancer showed no significant effect on the incidence of bladder cancer from the use of artificial sweeteners at this time (Morrison, 1980).

New models are now available which will permit further studies on the steps in the process of bladder carcinogenesis. Several procedures for the growth of differentiated bladder epithelium from single cells in culture are now available (Chalabowski, 1979; Leighton et al, 1980). In vivo procedures such as heterotopically transplanted rat bladder (Oyasu, 1979) and the ability to carry out ureterosigmoidostomy in rats (Rowland, 1979) are especially suited to study carcinogenic or cocarcinogenic factors in the urine. It has been shown in rats that one of the carcinogens in bracken fern is the flavone, quercetin, which is present in many plant products including fruits, vegetables, tea, spice, and sumac, which are consumed by man (Pamukcu et al, 1980).

Recent studies have shown that the normal blood-group antigens, known to be deleted from the cells of most in situ cancer, have been found to be absent in some normally appearing bladder epithelium from patients with extensive carcinoma in situ. It is proposed that areas of epithelium which appear benign according to conventional histologic criteria, but in which the blood group isoantigens are absent, may represent areas of low-grade carcinoma in situ (Weinstein et al, 1979).

Urinary tract cytology is of particular value in the detection of *in situ* bladder cancer in which visible lesions are not seen at the time of cystoscopy. One investigator has been intensively studying the cytology of voided urine samples from all patients seen on a large urology service (Farrow, 1979). He has been studying the factors in urine specimen handling and preparation that affect the quality of the ultimate cytologic preparation and consequently the accuracy of cytologic diagnosis. He has been relating the diagnostic accuracy of urine cytology to that of cystoscopy and has been correlating the clinical features of the patients examined with all available cytologic and pathologic specimens. Finally, he has been studying the evaluation of bladder cancer when detected in its early phases by urine cytology. His investigations are providing valuable information in all of these areas, particularly concerning the natural history of bladder cancer. He has shown that carcinoma *in situ* may persist for years before becoming invasive. His studies support the work of others who have suggested that there may well be two distinct forms of bladder cancer--the form in which tumors arise in a field of abnormal epithelium, and the form in which the tumor represents the only focus of preneoplastic epithelium in the bladder. Recognition of this concept is of great importance in the clinical management of bladder cancer cases or the possible development of screening programs for bladder cancer among high-risk groups.

In an effort to improve the accuracy of cytologic diagnosis of bladder tumors, one group of investigators is attempting to automate cytologic studies by applying computer-assisted methodology to the problem (Koss, 1979). In this system, exfoliated cells that have been previously smeared on a glass slide and stained are then scanned by a machine that feeds the information into a computer. It is hoped that this will one day permit more effective screening of slide preparations and reduce the level of human participation in cytologic studies of the urinary tract.

Another automated technique of studying bladder epithelial cells in the urine utilizes a flow-through system which permits the analysis of large numbers of cells in a very short period of time (Collste, 1979; Melamed and Mullaney, 1979). With appropriate staining or other treatment of the cells, the DNA and RNA content can be determined and a profile of the cellular content of the sample can be prepared (Darzynkiewicz, 1979). It is hoped that in conjunction with this analytic method, a cell sorter can be developed which would permit the collection for subsequent analysis of those cells which have been identified as clearly abnormal or neoplastic in appearance. The separation of these particular cells from others flowing through the system would permit further studies to be done on this selected subpopulation. These automated means of studying urinary tract cytology should help not only in the detection and diagnosis of bladder tumors, but in assaying the effects of therapy on tumor cells, assessing immunoreactivity in patients with tumors, and in experimental studies of carcinogenesis.

In the past, utilizing a carefully standardized model in the mouse using the carcinogen N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT), effective systemic agents such as *cis*-diaminedichloroplatinum (II) have been identified and subsequently shown to be effective in humans. More recently, it has been demonstrated by some investigators that this model can also be used to predict the efficacy of combined and intravesical treatment (Soloway and Murphy, 1979).

The mouse model has also raised the question as to the role that the transplantation of tumor cells into cauterized urothelium may play in subsequent recurrences of tumor (Soloway and Masters, 1980). In studies by other investigators, it has been demonstrated in rats that distilled water instilled into the bladder stimulates numerous mitoses of the epithelial cells (Weinstein et al, 1979). Since hypotonic solutions and distilled water are used frequently during cystoscopy, the possibility must be considered that such usage may also stimulate growth in the remaining foci of malignant or even premalignant cells.

Emphases and Projections

The information being derived from studies on bladder cancer carcinogenesis is providing the basis for promising new approaches which should be pursued. Information relevant to the development of assays is now available on chemical classes of bladder carcinogens, metabolism of these compounds, markers of preneoplastic lesions, and phases of the carcinogenic process. Worthy research objectives related to the development of assays may include: an in vivo and in vitro assay for bladder cancer initiators, a mechanism of screening for bladder cancer promoters, an in vivo and in vitro assay for bladder cancer promoters, a rapid test for bladder carcinogenesis based on markers of preneoplastic lesions, further improvements in methods for identifying known bladder carcinogens and their metabolites in urine, and further development of methods of testing in the urine or other body fluids for metabolites which have been related to bladder carcinogenesis.

The new information from laboratory studies as to the factors involved in the etiology of bladder cancer has increased the need for epidemiologic studies on various population groups. In many instances relating the proposed epidemiologic studies to laboratory studies will increase the understanding of each. In the rapidly developing area of bladder carcinogenesis, the format of some of these studies cannot be foreseen, but will include several case-control studies in which the effect of the use of promoters in a population with high incidence of bladder cancer is compared to that of a population with low incidence of this disease, and several cohort studies in populations with increased incidence of this disease in which the agent has not been identified. Identification of host factors which modify the incidence of this disease, include: laboratory studies in which genetic, biologic, or biochemical characterization of the host is related to the incidence of disease; and epidemiologic or clinical studies in which genetic, biologic, or biochemical characteristics of the host are related to the incidence of disease.

The demonstration that carcinogenesis of the urinary bladder is a multistep process, opens many potentially important areas of research which in the future may provide information on which the prevention of bladder cancer can be based. The recent finding that bladder epithelial cells can be grown in patterns similar to that of the urothelium through the use of unilateral air and nutrient gradients offers the possibility of conducting some of the carcinogenic steps in vitro. Many questions can now be addressed which previously were not possible. Examples of such questions are: "What is the relationship between an increased mitotic rate in the urothelium or hyperplasia and the

process of initiation? "How do such markers as pleomorphic microvillae, papilloma or hyperplastic nodules, localized changes in enzyme levels, or antigenicity relate to the initiation and promotion process? "What concentration levels are required for promotion? "How does the presence of a promoter modify the level of initiator required for tumor formation? "What factors enhance or extend the step of promotion? and "What compounds will inhibit promotion and what are the mechanisms of action involved?"

Animal studies should be conducted to determine if vitamin B_6 or vitamin A analogs will influence the promotional effect of tryptophan. Evidence from studies on individuals who have had tumors suggests that the administration of B_6 may reduce recurrence. Conducting similar studies on high-risk populations would be worthwhile.

It will be important to determine the role of seeding from papillary tumors in the genesis of carcinoma in situ away from the site of the primary tumor. The role of promoting factors in stimulating the progress of grade 1 papillary transitional cell carcinomas to tumors of higher grade must be determined. The practical implications are evident regarding clinical management. It is necessary to have the course of the disease under standard treatment adequately defined for suitably stratified populations of patients if new diagnostic procedures of treatment regimens are to be evaluated. The role of cytology in the proper management of superficial neoplasms of the bladder, especially in situ lesions, is so essential that continued efforts should be made to develop automated procedures for the identification of populations of cells in the urine or in bladder washings.

Enzymes should be sought which relate to the presence of lesions of the bladder. The encouraging initial studies of galactosyl transferase in the urine should be expanded. Even if the enzyme level proves not to be specific, as is the case of serum levels, this will still be a useful technique to monitor for recurrences if the sensitivity is high.

Attempts to isolate a tumor-associated antigen from the urine of bladder cancer patients has been encouraging. This would be a useful technique, and continued support of this area is proposed. Although the question as to whether a cell-mediated cytotoxicity common to many or all bladder cancer exists cannot be conclusively answered with present methods, the techniques relevant to cell-mediated cytotoxicity are developing rapidly enough that answers to this question may be possible in the next few years. It is proposed, that worthy projects be continued in this area, as it is related not only to detection and diagnosis, but also to the understanding and treatment of this disease.

At present, transurethral resection is suitable for small to moderate-size, localized, superficial lesions. When superficial lesions are multifocal or large, or field changes are present, this form of surgery is inadequate, and there is a need to develop an intravesical or systemic treatment less destructive than cystectomy. Results to date with thioTEPA are encouraging, but

other chemotherapeutic agents such as mitomycin are available and should be tried intravesically. In selected cases, even systemic chemotherapy would now appear to be justified. It is proposed that further projects be initiated to determine the role of immunotherapy in the management and treatment of superficial multifocal, high-grade disease.

Other Program Activities

In order to promote communication among investigators interested in cancer of the bladder and to provide timely and relevant discussions and reviews of aspects of this disease, an Investigators' Workshop was held in Sarasota, Florida on January 6-9, 1980. Major addresses were given on monoclonal antibodies, the etiology of bladder cancer, cell membranes, and DNA-RNA repair. Reports were made on the "International Case Control Study," supported through the NBCP, NCI, and the "Collaborative Study of Artificial Sweeteners," supported through the NCI and FDA. Evening discussion sessions were held to discuss the following research areas as they relate to cancer of the bladder: causality, host responses, and problems related to detection and diagnosis. A half-day session was held to review the information arising from the studies of Collaborative Group A.

NATIONAL BLADDER CANCER PROJECT
(Dollars in Thousands)

NONCOMPETING		COMPETING		TOTAL	
NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
26	$2,599	18	$2,440	44	$5,039

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Description

The National Large Bowel Cancer Project, with headquarters at The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, sponsors multidisciplinary basic and clinical programs of investigator-initiated research designed to examine the biology and promote the control of colon and rectal cancer. The research programs comprise a range of basic and clinical approaches to fundamental and applied problems conceived and conducted in an effort to achieve its primary goals. These objectives are pursued by encouraging research grants in a spectrum of programs designed to: 1) identify the causes, promoters, and inhibitors of large bowel cancer; 2) identify and clarify biochemical and molecular controls; 3) identify and characterize individuals at high risk; 4) promote screening, early diagnosis, and prevention of large bowel cancer; 5) apply innovative molecular and pharmacologic approaches in developing new chemotherapeutic treatments; 6) apply tumor immunobiology in the development of diagnostic markers, methods of treatment, and prevention of large bowel cancer; 7) develop clinical research treatment programs; and 8) develop resources, and promote interdisciplinary communications and collaborative research programs among grantees of the National Large Bowel Cancer Project.

Knowledge derived from these areas of investigation will have applicability in the design of sound research programs to improve management and treatment and thereby provide the basis for the control and prevention of this disease.

Accomplishments

Identification of Large Bowel Cancer Causes, Promoters, and Inhibitors

The endogenous formation of carcinogenic aliphatic azoxy compounds is under investigation. The colon carcinogen may be formed during the chemical oxidation of methyl-amine (Fiala, 1980). Using the organospecific colon carcinogen methyl-azoxymethanol (MAM), studies suggest that effects on RNA and protein synthesis are mediated by the proposed aldehydic metabolite. The inhibition of DNA synthesis appears to be an effect of the spontaneously derived carbonium ion, an effect unrelated to tumor induction (Grab et al, 1979). The colon microsomal system has been solubilized and resolved by column chromatography into its components: cytochrome P450 and cytochrome P450 reductase (Strobel et al, 1980). The activity in the colon is markedly increased by pretreatment with agastrointestinal hormones (Fang and Strobel, 1979). In other studies, sodium barbiturate and phenobarbital exhibited promotional effects on colonic tumor induction by dimethylhydrazine (DMH) in Lobund strain Sprague-Dawley rats (Pollard and Luckert, 1979). In addition to contributing to knowledge of colon carcinogenesis, metabolic capacity of the colonic drug metabolism system, and factors which control its activity, it may be possible to develop and evaluate strategies for improved chemotherapeutic management of colonic cancer.

At the molecular level, studies are being conducted to determine whether changes in processing of nuclear RNA take place in colon cells of mice treated with DMH. Methods are being developed to investigate RNA metabolism in colon carcinogenesis. A bank of RNA sequences, specifically expressed in mouse colon tumors and not in normal colon tissue, has been established to study abnormal expression of particular sequences as they relate to early detection. Utilizing limited nuclease digestion of nuclei from colon carcinoma cells, it has been found that ribonucleoprotein may be organized in a regular configuration, but that there is no simple repeating subunit structure analogous to the subunit structure of DNA and chromatin (Wahrman and Augenlicht, 1979). Exhaustive digestion of nuclear ribonucleoprotein in colon carcinoma cells reveals that hnRNA fragments of about 26 nucleosides are protected by proteins of 40,000 and 66,000 daltons in structures which sediment at 2S. Although these small RNA fragments are not of a simple, uniform sequence, they are a subset of all hnRNA sequences enriched in specific nucleotide sequences, thus providing the first evidence that the association of any protein with hnRNA is nonrandom with respect to nucleotide sequence (Augenlicht, 1979).

Cyclic nucleotides have been implicated as factors that can influence cellular proliferative activity and neoplastic transformation. Alterations in cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) metabolism have been demonstrated in human colonic carcinomas and acutely in normal colonic epithelium exposed to a direct-acting colon carcinogen, N-methyl-N'-nitro-N-nitrosoguanadine (MNNG) (DeRubertis et al, 1980). Modulation of the guanylate cyclase system of colonic epithelium by MNNG, antioxidants (butylated hydroxyanisole) and putative cocarcinogens (retinol, deoxycholate) may play a role in the expression of the oncogenic actions of MNNG in the colon (Craven et al, 1979). An understanding of the effects of these agents on colonic mucosal metabolism and of the role of local agents on proliferative activity in the colon mucosa is essential if rational and effective approaches to the control of this disease are to be developed.

An increased risk of developing large bowel cancer has been found to be associated with antecedent mucosal proliferative disease. This relationship is being explored in a model using transmissible murine colonic hyperplasia (TMCH) and DMH (Barthold, 1979; Johnson and Barthold, 1979). Studies show that TMCH promotes the early phases of DMH carcinogenesis by reducing the latent period of DMH atypia and enhancing the sensitivity of the mucosa to single subthreshold doses of DMH. The DMH-TMCH model allows the sequential study of focal atypia arising from single doses of DMH, and has revealed that atypia regress despite their cytokinetic and ultrastructural similarities to overt neoplasia.

Continued efforts are being aimed at elucidating the metabolic activities of the gut microflora in an effort to better understand the potential role of the intestinal microflora in the genesis of large bowel cancer (Mastromarino, 1979). Metabolic epidemiologic studies and evaluation of fecal mutagenic activity in healthy controls and in low- and high-risk subjects are being conducted in an effort to identify compounds and biochemical processes that may be related to the etiology of human colon cancer (Reddy, 1979). Additional suggestive evidence for the promoting effect of bile acids on colon tumorigenesis has been observed in male F344 rats treated with N-methyl-N-nitrosourea (MNU) and either cholic acid (Cohen et al, 1980) or chenodeoxycholic acid (Sarwal et al, 1979).

The protective effect of plant sterols against chemically-induced colon tumors in rats has also been reported (Raicht et al, 1980).

A number of grantees are conducting research programs aimed at delineating the identity of a colon carcinogen and the factors that contribute to its formation and activation. One approach involves determining the presence of fecal mutagens using the Ames assay. A mutagen produced during anaerobic incubation has been characterized, and analysis suggests that the mutagen is probably not an N-nitroso compound, and can be stabilized with the addition of antioxidants. Addition of the S9 mammalian microsomal fraction decreased the mutagenicity of fecal mutagens, as did crude preparations of beta-glucuronidase from several sources (Aswell et al, 1979). The data suggest that the anaerobic fecal flora is involved in mutagen production. Increasing the amount of fecal mutagen by anaerobic incubation may permit determination of its structure and, possibly, the identification of the environmental precursor. These data may represent the first demonstration that a mutagenic and possibly carcinogenic compound is produced at the site of action. The possible involvement of the anaerobic bacteria in the in vitro production of mutagens suggests that if the responsible species can be identified, appropriate antimicrobial agents might be used to prevent the occurrence of the disease and provide a strategy for the prevention of colon neoplasia.

The relationship between diet and the etiology of large bowel cancer is under intense investigation. The effects of diet, antibiotics, and supplements of Lactobacillus acidophilus on DMH-induced intestinal tumors in rats (Goldin and Gorbach, 1980) and on human fecal bacterial enzymes (Goldin et al, 1980) have been investigated. Supplements of Lactobacillus increased the latency period of DMH-induced adenocarcinomas of the colon (Goldin and Gorbach, 1980). The relationship of diet to colon cancer is also being investigated by isolating and identifying mutagens/carcinogens resulting from the cooking of meats and other products, utilizing mutagenicity tests to separate the active principles (Weisburger and Spingarn, 1979). The isolation of a primary mutagen from beef has been achieved (Spingarn and Weisburger, 1979). A molecular formula has been assigned and synthetic work has been initiated to establish the definitive structure, which will permit bioassay determination of whether mutagenicity represents carcinogenicity in the colon. It has also been determined that several breakdown products of glucose react with ammonia and have mutagenic activity (Spingarn et al, 1980). Thus, both meat and starchy foods have the potential to produce mutagens during the cooking process. By studying the mechanism by which these substances are formed in cooking, it may be possible to develop a strategy for inhibition.

The possibility that nitrite and nitrate are formed de novo in the intestine, possibly by heterotrophic nitrification, has been demonstrated, suggesting that nitrite may play a role in the etiology of intestinal cancer (Gomez et al, 1980). Understanding the source of the nitrite or nitrosating agent(s) may provide a means to control the process of carcinogen formation and/or screening for high-risk individuals and a basis for interpreting the correlations from epidemiologic studies between diet and colon cancer incidence. Experiments aimed at inhibiting carcinogen-induced neoplasia of the large intestine are also being conducted (Wattenberg and Sparnins, 1979). Studies on the possible mechanism of inhibition of MAM acetate-induced neoplasia of the large bowel demonstrate involvement of NAD+/-dependent alcohol dehydrogenase of the large

bowel and liver, the system postulated to activate MAM to its ultimate carcinogenic form. Other studies including the effects of trace elements, fiber, and antioxidants on chemical-induced colon carcinogenesis are also under investigation (CA25699, CA25509, CA25886). These approaches offer potential for application to the prevention of large bowel cancer in man.

Identification and Clarification of Biochemical and Molecular Controls of Large Bowel Cancer

A recent, important contribution has been the developement of methodology for long-term tissue culture of human colonic carcinoma using density gradient centrifugation on Percoll. The conditions required for initial growth of most malignant epithelial cells have been determined. Isolation of subpopulations of cells from cultures of a single colonic carcinoma with different functional properties as assessed by in vitro markers for malignancy, and transplantation into athymic nude mice have also been described. A subpopulation of 5-fluorouracil-resistant malignant cells from a culture of human colonic carcinoma has been isolated. These variant cells are capable of forming metastases (Kimball and Brattain, 1980). A maturation-induction model using human colon cancer cells as targets has been described (Dexter and Hager, 1980). N,N-dimethylformamide (DMF) reversibly induced in cultured colon cancer cells a less malignant phenotype with concomitant maturation effects. The relationship between cancer and differentiation should provide a better understanding of the biology of human colon carcinoma. Moreover, the existence of tumor cell markers and the potential reversibility of tumor growth behavior may form the basis for new approaches to diagnosis and colon cancer treatment. Loss of attenuation of the malignant phenotype has been observed when tumor cells are treated with sodium butyrate which inhibits histone deacetylase activity, thus allowing the histones to accumulate in their hyperacetylated forms (Sterner et al, 1979). One consequence is to weaken the interactions of the histones with the phosphate groups of the enveloping DNA strand, making it more accessible to nucleases and presumably to RNA polymerizing enzymes. Inhibition of the high mobility group protein deacetylase activity by butyrate, favors the release of constraints upon the associated DNA sequences (Sterner et al, 1979a).

The effects of sodium butyrate and dimethyl sulfoxide on the biochemical properties of human colonic adenocarcinoma cell lines in culture have been reported (Kim, Y.S. et al, 1980). Topographic studies have been initiated using lectins as specific molecular probes to define the labeling patterns of carbohydrate-containing components of colonic goblet cells. Alterations in the structure of membrane mucin glycoproteins in colonic cancer have also been determined and localized (Kim, Y.S. et al, 1979). Identification, isolation, and characterization of tumor-associated or tumor-specific cell surface membrane glycoproteins or glycolipids of homogeneous cultured human colon cancer cell lines will be useful, not only as diagnostic tumor markers, but in providing an explanation of the molecular processes involved in malignant transformation, growth control of cells, and metastasis.

The molecular basis of malignant transformation in cells of the colonic epithelium exposed to DMH has been investigated. DMH induction of colonic tumors in rodents is accompanied by alterations in the composition and metabolism of DNA-binding proteins in the nucleus and by abnormal postsynthetic modifications of

chromosomal proteins (Allfrey et al, 1979). Parallel investigations have focused on postsynthetic modifications of proteins at early stages in carcinogenesis with attention to protein phosphorylation (Boffa et al, 1979). New methods have been developed for the isolation and recovery of proteins which have been phosphorylated (Sun et al, 1980).

Abnormalities of DNA synthesis during the development of carcinoma, the components and molecular processes involved in chromatin replication during carcinogenesis, and changes occurring in gene regulatory control systems which permit perpetual division of cancer cells have been investigated. Changes in the immunospecificity of chromosomal nonhistone proteins arising during the process of chemical carcinogenesis have been identified (Chiu et al, 1979). Changes in the immunospecificity of the nonhistone protein DNA complexes in the colon of rats treated with DMH occur as early as the fourth week after treatment (Chiu et al, 1980). The appearance of the tumor-specific nuclear antigen can be abolished by simultaneous treatment with disulfiram. Continued study of the DNA replication in normal and in neoplastic colorectal epithelial chromatin may reveal abnormalities in the DNA synthetic control elements associated with colon cancer.

Studies are in progress to study DNA repair, its regulation, and its importance in carcinogenesis and in tumor therapy. DNA repair in colon cells has been compared with other cell types and the local factors which effect specific inhibition of DNA repair have been investigated (Cantrell et al, 1979). Expanding knowledge of the cellular and molecular mechanisms that regulate cell division in normal and malignant cells opens new possibilities for improved diagnosis, prognosis, and treatment of large bowel cancer.

Identification and Characterization of Individuals at High Risk

Screening programs would appear to be most effective in high-risk populations. Consequently, emphasis has been placed on the identification and characterization of high-risk individuals, e.g., patients with familial polyposis coli or hereditary adenomatosis of the colon and rectum (ACR), an autosomal dominant trait. It has been demonstrated that transformation-related phenotypic expressions in skin fibroblasts derived from normal appearing biopsies of tumor-prone and tumor-bearing individuals with ACR are extensive (Kopelovich, et al, 1979). Perturbation of these cells by tumor viruses (Kopelovich and Sirlin, 1980) or tumor promoters might aid in elucidating the mechanisms involved in the control of tumorigenicity and in the analysis of genetic predisposition to cancer in man.

The influence of a germinal mutation in the genome of cultured cells to the risk of somatic mutations and transformation to cancer cells is being assessed (Danes et al, 1979). The technology for establishing and maintaining colonic epithelial and fibroblast cultures from individuals with and without ACR is being developed. The study of cultured cells from ACR patients in its variant forms has demonstrated that the cellular abnormality is presumably due to *in vitro* expression of the mutant genotype (Danes and Alm, 1979; Danes et al, 1979). If clinical cancer arises through a series of alterations in the genome, monitoring changes in biological activity of cultured cells with and without known germinal mutations should help elucidate their role in normal and cancer cell

differentiation. Research is being directed at elucidating the basic mechanisms of action of the genetic defect associated with heritable colorectal cancer and defining the phenotypic expressions of preneoplasia that may identify carriers of the gene before clinical symptoms appear (Naylor et al, 1979). Skin, blood, colonic lavage, and intestinal biopsies are under study for their potential in identifying and characterizing these high-risk individuals. Work is continuing on characterizing extracolonic manifestations of the syndrome (Gardner, 1979).

Screening, Early Diagnosis, and Prevention of Large Bowel Cancer

Although the ultimate goal is primary prevention of human large bowel cancer, particular attention is being paid to secondary prevention through screening, early detection, and follow-up programs of high-risk individuals. The feasibility of selecting patients at risk for colorectal cancer by testing for occult blood by using the Hemoccult II slide test is being evaluated in a double-blind study (Winawer, 1979; Winawer, 1980). The sensitivity and specificity of the diagnostic techniques are being evaluated (Winawer, 1979a; Winawer et al, 1979), including rigid sigmoidoscopy compared to flexible sigmoidoscopy. Results of the compliance studies to be completed this year will have important relevance to motivating populations for screening. Establishing the criteria and the value of screening to identify individuals with occult neoplasms should lead to the identity of earlier lesions which are more amenable to treatment.

Efforts to develop and evaluate quantitative biochemical procedures for the early detection of large bowel cancer are being carried out by identifying the presence of retinoic acid-binding proteins (RABP) and dihydrotestosterone in murine and human colon tumors (Sani et al, 1980). A high percentage (80 percent) of human colon, cecal, and rectal tumors analyzed contained RABP in detectable amounts. The measurement of binding protein levels in clinical specimens of colon tumors may prove useful as biochemical markers of human malignancy.

Zinc glycinate marker (ZGM) is a distinct antigen isolated from colon carcinoma liver metastases, and has been demonstrated by cytochemical staining to be produced by the epithelial cells of the GI tract (O'Brien et al, 1979). ZGM analyses are complementary to CEA and may improve the usefulness of CEA for initial diagnosis and staging of colorectal cancer.

Application of Molecular and Pharmacologic Approaches in Developing New Chemotherapeutic Treatments

Using a variety of systems, new molecular and pharmacologic approaches to improved treatment of large bowel cancer are being fostered. The thermosensitivity of cultured human colon adenocarcinoma cells (Lo Vo) has been investigated (Barlogie, et al, 1980). Enhancement of drug-induced cell kill by moderate hyperthermia suggests that thermochemotherapy should be evaluated clinically.

Biochemical studies of the inhibition of enzymes of key significance to the de novo and salvage pathways of uridine 5'-mono-phosphate (UMP) have been evaluated (Ahmed and Welch, 1979). The kinetic requirements for the accurate determination of human uridine-cytidine kinase activity in human colorectal adenocarcinomas are being investigated. Using rectal adenocarcinomas maintained

as xenografts in immune-deprived mice, the common factors among six tumors that respond individually to a spectrum of clinically used agents have been under intense investigation, concentrating primarily on the fluorinated pyrimidines (Houghton et al, 1979). Another in vitro approach has been the use of multicellular tumor spheroids, formed from several lines of human colorectal adenocarcinoma cells grown in continuous culture. New techniques have been developed that facilitate the growth and handling of these spheroids (Woodman and Armour, 1979).

The selective inhibition of colon tumor protein synthesis by sodium cyanate is under study. A reproducible assay system for the analysis of the cyanate effect has been developed. While cyanate alone has no effect on protein synthesis, once activated, it exerts an inhibitory effect on tumor protein synthesis, while thiocyanate does not. Inhibition of thymidine incorporation was not observed, arguing against a general toxicity (Boffa et al, 1979; Allfrey et al, 1979). This approach may lead to the design of chemotherapeutic agents which will selectively block protein synthesis in malignant cells without comparable toxicity to normal host tissues. Efforts are also being directed to enhance the effects of known agents through judicious combination chemotherapy based on knowledge of mechanisms of action of the specific agents. Quinazoline analogs of folic acid are being evaluated alone and in combination with 5-fluorouracil inhibitors for their potential in the treatment of human large bowel adenocarcinoma (Bertino et al, 1979).

Model systems for biological, biochemical, and pharmacokinetic studies are being developed to better understand the nature and behavior of colon cancer in man (Corbett et al, 1979). A series of new transplantable colon tumors have been developed and biologically characterized to better simulate the heterogenous characteristics of human colon adenocarcinoma (Cowen et al, 1980). The development and improvement of quantitative techniques for measuring treatment effectiveness on apparent or subclinical disease are being emphasized.

Application of Tumor Immunobiology in the Development of Diagnostic Markers, Methods of Treatment, and the Prevention of Large Bowel Cancer

A glycoprotein, secretory component (SC), is a cell-surface receptor for dimeric IgA and is located on the basolateral surface (Brown, 1980); whereas, CEA is normally expressed in the apices of intestinal epithelial cells. However, among eight moderately to poorly differentiated colon cancers, the surface distribution of CEA is abnormal in malignant colonic epithelial cells, and the degree of surface polarity correlates with the degree of morphologic differentation (Ahnen and Brown, 1980). The inability to establish and maintain the polar distribution of glycoproteins might be a feature of undifferentiated malignant neoplastic cells.

A metastatic model simulating the natural history of the human disease has been established. The characteristics of the model are being compared and contrasted with the subcutaneous transplant of the same cell line (Leveson et al, 1979; Goldrosen et al, 1979; Goldrosen, 1980). In this model, hepatic metastasis is a late occurring event and the presence of regional mesenteric node antitumor response, as measured by leukocyte adherence inhibition (LAI) assay, correlates

with the absence of hepatic metastasis, supporting the concept that breakdown in the local-regional response plays a permissive role in progressive tumor growth and formation of metastases (Goldrosen, 1980). To elucidate factors that contribute to the breakdown of the specific antitumor response, studies were initiated to define the types of mononuclear cells involved in the LAI response (Goldrosen et al, 1979). It appears that a specific LAI response which is dependent upon an interaction between sensitized B-cells and tumor antigens to produce a soluble antibody-containing mediator, can be abrogated by suppressor T-cells and serum-blocking factors. The role of immune response in the metastatic process in colorectal cancer suggests new avenues of immunotherapy based on the specific stimulation of the local-regional immune response.

Knowledge about the immune response to antigens associated with bowel carcinoma from the rat is progressing (Sjogren, 1979). Efforts have been directed at solubilizing and purifying cell surface membrane antigens in rat colorectal carcinomas with the aim of making use of the antigen as a target in immune assays for antigen and specific antibodies, and as purified immunogen in immune manipulations. Continued effort has been directed at developing more efficient and selective noncytolytic surface membrane techniques (Kahan et al, 1979). The feasibility of using detergent-solubilized membrane antigens incorporated into liposomes for in vivo immunizations has been established (Sjogren, 1980). Efforts to separate lymphocyte/monocyte populations are important for analyzing the immune status of the tumor-bearing host in more detail, and providing a basis for proper assay of specific lymphocyte cytotoxicity. In addition, it creates a basis for immune manipulation. Monoclonal antibodies specific for human colon cancer cells have been obtained, and it has been demonstrated that colon tumor antigens solubilized by 3M KCl are reactive with this monoclonal antibody.

Continued efforts have been employed to identify, isolate, purify, and characterize tumor-associated and organ-associated antigens of human colonic tumors. Colonic carcinoma xenografts utilizing both hamsters and nude mice, and cell cultures are being used. The markers may have immunodiagnostic or immunotherapeutic significance. Elucidation of the immunochemistry and immunocytochemistry of colon-specific antigen (CSA) and colon-specific antigen protein (CSAp) have been pursued (Pant and Goldenberg, 1979). It has been demonstrated that CSAp is distinct from other tumor-associated substances of the colon and is quantitatively increased in colonic cancer, and in certain inflammatory bowel lesions compared to normal adult colon (Goldenberg, 1979). Since CSAp is distinct from other colon antigens described to date, these studies provide an opportunity for the development of assays of colonic cancer detection or of colonic cancer treatment, using CSAp as a selected target for radiolabeled antibodies.

Research efforts continue on the characterization and distribution of CEA (Frackelton and Weltman, 1980; Egan and Go, 1979; Coligan and Slayter, 1979; Shively and Todd, 1979). Efforts have been primarily directed at enhancing the clinical utility of CEA by studying its structure and its relation to the disease state. Another antigen tumor extract (TEX), found in hepatic metastases of colonic adenocarcinoma, is closely related to CEA and to NCA, and is currently under investigation. TEX differs from CEA in its carbohydrate content. The amino acid sequencing techniques for CEA and related antigens have been improved (Shively et al, 1979; DelValle and Shively, 1979). Currently, the clinical utility of CEA as a serodiagnostic tool is in follow-up of patients for

recurrence, but its application to improved diagnosis and to specific therapy using anti-CEA antibodies for tumor localization remains for future evaluation.

Clinical Research Treatment Programs

In view of the poor response rate of colon tumors to 5-fluorouracil, the most widely used chemotherapeutic agent, efforts have been aimed at improved response rates. Proposals with novel and/or innovative therapeutic or preventive approaches have been encouraged. Based on experimental evidence that antioxidants retard carcinogenesis, a phase III randomized double-blind study of ascorbic acid, 3/gm/d has been completed at St. Mark's Hospital in London (CA23760). Analysis of the data is in progress; however, it appears that ascorbic acid treatment has a modest effect on reduction of rectal polyps in patients with familial polyposis coli who have undergone colectomy and ileorectal anamosis. This trial may offer promise for chemoprevention of large bowel and should form the basis for improved intervention studies.

A feasibility study to evaluate the effectiveness of transfer factor in the treatment of patients with large bowel cancer is currently in progress (CA22374). The LAI assay to measure cell-mediated immunity and blocking factors has been improved with the use of cryopreserved mononuclear cells as a substitute for fresh leukocytes.

Follow-up and critical analysis of patients with Dukes' C large bowel cancer treated with systemic BCG or BCG and 5-fluorouracil continues (Mavligit et al, 1979). The two adjuvant arms appear to be equally efficacious for survival. After more than six years, the median survival of patients in the adjuvant therapy groups is 62 months versus 46 months for historical controls.

In an additional innovative approach to therapy, it is being determined whether tumor-localizing antibodies to CEA combined with a neutron-capturing agent (boron) are useful for selective, slow neutron irradiation of CEA-producing tumors of human origin grown in hamsters (Kim, E.E. et al, 1980). While the approach thus far appears feasible in animals, a mixture of antibodies directed against more than one tumor-associated antigen--for example, CSA and CEA--shows better tumor localization than antibodies to CEA alone.

Developing Resources

To help elucidate the possible involvement of bile acid metabolites in the promotion of human large bowel cancer, resources of purified synthetic reference standards are being prepared and distributed to interested investigators (Chang, 1979). Improved methodologies in the identification of bile acid derivatives have been developed using gas chromatography-mass spectrometry-computer storage, thus providing greatly improved resolution and separation of the bile acid derivatives (Elliott, 1980).

An additional resource has been established at the American Type Culture Collection. Human and experimental colon tissues are being collected to establish a cell bank for large bowel cancer research. The cell lines will be expanded and characterized and, if certified, made available for distribution to interested investigators (Hay, 1979).

Emphases and Projections

A major emphasis has been on programs aimed at preventing large bowel cancer. These programs have primarily been directed toward: 1) assessment of "high-risk" populations and dietary factors believed to exert an influence on large bowel carcinogeneses; 2) development of immunological approaches; and 3) examination of currently identified and new drugs which may interfere with the carcinogenic process. The research goals of the NLBCP are the acquisition and application of knowledge directed toward the ultimate control (treatment and prevention) of large bowel cancer through the following objectives: 1) elucidation of the etiologic and modifying factors associated with human large bowel cancer; 2) elucidation of the processes that control the behavior of normal and malignant cells; 3) identification of the factors that mediate the conversion of cells from normal to malignant states, and their mechanisms of action; 4) development and evaluation of advances in screening, diagnosis, and therapy of large bowel cancer; 5) identification of the properties of malignant cells with special emphasis on their vulnerabilities, and development of therapeutic agents and procedures that exploit those vulnerabilities with the greatest possible sparing of normal cells; 6) elucidation of the tumor-host interaction with emphasis on understanding and augmenting the body's defense systems against cancer cells; 7) improvement of cell-culture techniques and establishment of normal colonic epithelium in culture; 8) development of pilot studies to assess novel and/or innovative therapeutic or preventive approaches for large bowel cancer; and 9) application of new knowledge to the benefit of the patient as rapidly and as effectively as possible.

Model systems, now well developed, are expected to expand our concepts and knowledge concerning large bowel cancer. Such models are now being used to: 1) identify and test new anticancer drugs, 2) identify potential inhibitors of carcinogenesis, 3) develop approaches to immunoprevention, 4) discern factors associated with transformation of colon epithelium to precancerous lesions and carcinoma of the large bowel, and 5) assess the influence of dietary factors and the microflora in the initiation, promotion, or inhibition of large bowel cancer.

Methods derived from research in cellular biology will be utilized to ascertain alterations in cellular behavior and to identify phenotypic expressions characteristic of high-risk individuals. Identification of cellular and biochemical properties related to growth and metastatic potential of large bowel cancer will be encouraged. Programs in screening and early diagnosis of large bowel cancer will also be encouraged with particular emphasis on evaluating the factors affecting their implementation and efficacy.

The NLBCP will foster development of new chemotherapeutic drugs to treat large bowel cancer. Research will be pursued to identify targets dealing with metabolic pathways involved in nucleic acid and protein synthesis. Cell surface glycoproteins and fundamental studies of membrane structure will be continued to uncover abnormal, exploitable, cellular functions.

Other Program Activities

The seventh workshop sponsored by the NLBCP in January 1980 was entitled "Bile Acids and Large Bowel Carcinogenesis." Basic scientists, clinical investigators

and physicians met and discussed many aspects of this topic, including analytical methods of bile acid determinations, the physiological role of bile acids, and bile acids in colon carcinogenesis. A summary of this workshop is available upon request.

A planning committee met in May 1980 to consider specific topics for the 1981 workshop to be held January 8-10, in Dallas, Texas. In addition to evaluating the scientific accomplishments of the NLBCP, the workshop will identify critical areas of research needs, develop priorities for future research strategies, stimulate new approaches to large bowel cancer research, and promote communication and exchange of information between clinical investigators and basic scientists.

The Cell Bank for Bowel Cancer Research established at the American Type Culture Collection, Rockville, Maryland, has received twenty-four cell lines derived from human colorectal tumors including one cell line (CMT93) from a chemically-induced tumor of the mouse. The human cell lines include: LoVo; SW48, 403, 480, 620, 707, 802, 837, 948, 1116, 1222, 1417, 1463; COLO 201, 205, 320D HSR, 321 HSR; WiDr; HuCCL-14; ME(ACR^{+}-S), PF (ACR^{+}-AS); DLD1 and HCT15. The cell lines are in various stages of characterization. A committee has been organized which has responsibility for examining the characterization of the cell lines banked before their release to the general scientific community. After certification of the lines by the Committee, their availability will be announced in the NLBCP and Tissue Culture Association Newsletters.

NATIONAL LARGE BOWEL CANCER PROJECT
(Dollars in Thousands)

Noncompeting		Competing		Total	
No.	Amount	No.	Amount	No.	Amount
48	$5,100	5	$592	53	$5,692

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NATIONAL PANCREATIC CANCER PROJECT

Description

The National Pancreatic Cancer Project, an organ site program headquartered at Louisiana State University Medical Center, is a coordinated research effort which sponsors basic and clinical research in the areas of epidemiology, experimental biology, diagnosis, immunology, pathology, and treatment. Basic research is encouraged in order to provide information about the natural history of the disease, and therefore studies of carcinogenesis and cell biology are supported. Little information about the epidemiologic implications of pancreatic carcinoma is available, so studies examining socioeconomic, environmental, and dietary factors are an important part of the research program. Early diagnosis of the disease is still a problem, although in recent years several techniques including laparoscopy, scanning, and ultrasonography have been under investigation and show some promise. Further studies of tumor markers and immunodiagnostic tests are needed. Now in its sixth year of operation, the National Pancreatic Cancer Project is currently supporting twenty-eight research projects, with six additional projects approved and recommended for funding. To date, 179 grant applications have been reviewed and fifty-eight have been funded.

Accomplishments

Studies on the alteration of biochemical and immunological characteristics of the plasma membrane of neoplastic cells as compared with their normal counterparts are of considerable interest. Chu et al, (1979) studied protease activity in the plasma membrane fraction isolated from the primary pancreatic tumor, its liver metastasis, and normal tissues of a pancreatic cancer patient. Inhibitory studies with a variety of protease inhibitors were conducted to characterize partially the membrane protease of the primary pancreatic tumor.

The bovine pancreatic duct provides a useful experimental model system for the study of pancreatic carcinogenesis. Kahng et al, (1979) have demonstrated the presence of aryl hydrocarbon hydroxylase in bovine pancreatic ducts and inducibility of this enzyme by polycyclic aromatic hydrocarbons *in vitro*. A method has been developed recently for the use of bovine pancreatic ductal explants in chemical carcinogenesis as well as in physiological studies. Selected plasma membrane enzymes in the bovine main pancreatic duct have been measured and compared with the same enzymes in bovine acinar preparations (Lakshmanan et al, 1979). All enzymes studied demonstrated higher levels in the duct per milligram protein than in the acinus. Nitrosoureas are active therapeutic agents against a number of experimental and human neoplasms. Recently, experiments have been undertaken which provide information on the relationship between nitrosoureas and the chromosomal enzyme poly(ADP-ribose) polymerase (Sudhakar et al, 1979). Because of the differential effect of nitrosoureas on this enzyme, the interaction of these agents with precise regions of nucleosomal chromatin was investigated.

DiMagno et al, (1979) developed a canine model that allows for the simultaneous monitoring of pancreatic and duodenal pressures, pancreatic enzyme and biliary secretions, and duodenal motor activity. In this study, the relationships of total duodenal volume flow, bile secretion, pancreatic secretion, and pancreatic duct pressure to duodenal phase III activity are reported.

The role of lysosomal enzymes in the invasion of normal tissue by rapidly growing tumors is well documented. Chronic alcoholism, which has been reported to predispose individuals to pancreatic cancer, may bring about early biochemical changes in the pancreas that are reflected in the concentration or type of lysosomal enzymes present in pancreatic secretions. Rinderknecht et al, examined pure human juice obtained by direct cannulation of the main pancreatic duct of 11 healthy volunteer subjects and 10 chronic alcoholics without detectable pancreatic disease. The investigators speculate that the apparently selective increase in acid hydrolase activities indicates either increased synthesis or increased release of these proteins from the pancreas of chronic alcoholics compared to normals. They hypothesize that this difference may be relevant to the development of pancreatic cancer.

Keller et al, (1979) performed an experimental study, the objective of which was, to improve and make safer retrograde pancreatic venography by temporarily reducing visceral arterial flow, a technique of proven clinical value in epinephrine renal venography. The authors concluded that integrated visualization of the pancreatic venous circulation comparable to that achieved through epinephrine renal venography is not feasible with safety. They suggest that where visualization of the pancreatic veins is indicated, it is best done by selective catheterization of multiple pancreatic branches.

The measurement of lactoferrin concentrations in pure pancreatic juice may be useful in the diagnosis of pancreatic diseases. Fedail et al, (1979) measured lactoferrin in pure pancreatic juice by radioimmunoassay. Lactoferrin concentrations were found to be high in pancreatic juice from patients with chronic pancreatitis, but considerably lower in juice from control subjects and patients with carcinoma of the pancreas.

The development during the past few years of immunologic assays for detecting various tumor-associated antigens has facilitated the diagnosis and management of gastrointestinal cancers. Schultz and Yunis (1979) report that they now have an antiserum that appears to selectively react with an antigen in pancreatic cancer extracts. The antigen was detected in the sera of patients with biopsy-confirmed pancreatic cancer, although it was also found in the sera of a small number of patients with other neoplastic and non-neoplastic diseases. Chu et al, (1979) have identified and isolated a glycoprotein antigen from ascites fluid of pancreatic cancer patients. At present, immunoassays are being developed for its clinical application. Recent studies have evaluated a modified leukocyte adherence inhibition assay (LAI), the microLAI assay, as a specific immunodiagnostic test for the presence of pancreatic cancer (Goldrosen et al, 1979; Douglass et al, 1979). According to these publications, the micro-LAI appears to be immunologically specific and reproducible,

and has a good potential as an immunodiagnostic test for pancreatic cancer.

Several studies have suggested that pancreatic cancer in humans may be etiologically related to exogenous chemicals. Longnecker et al, (1980) did a histological evaluation of a series of prospectively collected human pancreases for the presence of acinar cell and ductal lesions. The incidence of nodules was found to be higher among patients with a history of heavy cigarette smoking than among nonsmokers, and among patients with a history of alcohol abuse than among abstainers. Although acinar cell nodules of the pancreas have been described in rats given carcinogenic chemicals, similar nodules have not been reported in humans until recently. Two cases of nodular acinar cell lesions in the human pancreas have been described by Shinozuka et al, (in press). The possible significance of a history of heavy alcoholic intake and cigarette smoking in the genesis of atypical acinar cell nodules remains to be established.

The carcinogenic effects of N-nitroso-bis(2-hydroxypropyl)amine (BHP) in organ-cultured embryonic rat pancreas were demonstrated by direct addition of BHP to the culture medium and by the transplacental route followed by organ culture (Parsa et al, 1979). Both methods appeared efficient for in vitro induction of adenocarcinoma. Transplacentally, BHP failed to produce any pancreatic tumor in vivo. Parsa et al, (in press) have worked out a two-stage model of chemically induced pancreatic carcinoma. It features a short latent period (6-10 weeks) which allows for a more facile investigation of the carcinogenic process and the factors affecting it.

Rao and Reddy (1979) describe a transplantable acinar cell carcinoma which will be useful in the delineation of differences between normal pancreatic acinar cells and malignant acinar cells both morphologically and functionally. The study by Reddy et al, (1979) on the surface morphology and agglutinability of isolated normal and neoplastic rat pancreatic acinar cells indicates that tumor cells are more susceptible than normal acinar cells to agglutination by Concanavalin A. Reddy et al, (1979) have outlined the developments that have occurred during the past five years in the relatively new field of experimental pancreatic carcinogenesis.

Emphases and Projections

Since the establishment of the organ site program for the pancreas, a substantial amount of progress has been made toward a better understanding of pancreatic carcinoma. Investigators have been encouraged to focus on treatment, etiology (including epidemiology, cell biology, and carcinogenesis), early diagnosis, and pathology. Treatment has been identified as a top-priority research area, and several studies are beginning in this area, including a study of intraoperative radiation therapy; phase II studies of combination chemotherapy (including 5-fluorouracil, adriamycin, mitomycin-C, and chlorozotocin); and a study involving interstitial implantation of radioactive sources in combination with external radiotherapy and adjuvant chemotherapy with 5-fluorouracil.

Little epidemiologic information on pancreatic cancer is available, and well-designed case-control studies testing specific hypotheses regarding the causes of pancreatic cancer are needed. Additional work is needed to document the incidence of spontaneous pancreatic tumors in experimental animals, and a continued search will be made of chemicals which produce pancreatic adenocarcinoma.

Early diagnosis continues to be an important research area, with an emphasis on tumor markers, scanning techniques, uptake studies, and immunological studies. The standardization and improvement of available methods to diagnose pancreatic cancer are also needed.

Additional priority research areas include study of the pathology of precancerous lesions in the human pancreas, and the development of an acceptable clinicopathologic classification of pancreatic cancer.

Other Program Activities

The National Pancreatic Cancer Project sponsored its fourth annual joint meeting with the American Pancreatic Association in Chicago on November 1 and 2, 1979. The open meeting, attended by over 220 scientists and clinicians involved in pancreatic cancer research, featured 50 papers, including presentations by 20 grantees of the Project. Each year this meeting has been expanded, and the increasing quality of research is evident. A fifth joint meeting is planned for November 6 and 7, 1980 in Chicago. On October 4, 1979, the Project sponsored a workshop on Animal Tumor Models for Pancreatic Cancer to allow an exchange of data and ideas. At present, the Project supports six investigators with established animal models who presented their work along with other experts in the field. The papers and discussions of the meeting have been compiled into a booklet which is available upon request. An International Meeting on Pancreatic Cancer was held in New Orleans on March 10 and 11, 1980, in an attempt to bring together the major disciplines and key investigators in the field of pancreatic cancer research. The total attendance was 217, including 43 invited speakers. Participants came from 33 states and 5 foreign countries. The proceedings will be published as a supplement to the journal Cancer. A Radiation Therapy Workshop was held on April 18, 1980 in New Orleans, with emphasis on the most recent radiotherapeutic approaches to pancreatic cancer. The proceedings of this meeting will be published in Cancer Clinical Trials.

A special issue of Seminars in Oncology, guest edited by the Project Director, came out in September 1979. This issue contains eleven articles covering clinical advances in the field of pancreatic cancer including diagnosis, epidemiology, pathology, tumor markers, and treatment. The majority of the contributions came from individuals associated with the Project.

A Project Newsletter is published semiannually and includes: progress reports by grantees, an extensive bibliography of current articles related to pancreatic cancer (with abstracts of selected citations), and information for prospective grant applicants. This Newsletter is sent to approximately 1000 individuals on a continuing basis, and is available upon request.

(Dollars in Thousands)

NONCOMPETING		COMPETING		TOTAL	
NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
23	$1,298	4	$ 502	27	$1,800

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Description

Carcinoma of the prostate is the second most common site of cancer in men, accounting for 17 percent of malignant tumors occurring in U.S. males. The prostate cancer-related death rate (15 deaths annually for every 100,000 U.S. males) has not changed significantly over the past thirty years. In 1979 an estimated 64,000 new cases of prostatic cancer were diagnosed and over 21,000 deaths of American men are expected from this disease. In spite of these figures, prostate cancer has been the subject of only limited clinical and laboratory research through the early 1970's. In response to the need for a comprehensive and coordinated research effort, the National Prostatic Cancer Project (NPCP) was activated in 1973, with headquarters at Roswell Park Memorial Institute, in accordance with the objectives of the National Organ Site Program. The Project has developed a research program that encompasses the areas of Etiology and Prevention, Detection and Diagnosis, and Treatment of prostatic cancer. The pursuit of targeted research through investigator-initiated efforts has resulted in application of a broad spectrum of experimental research disciplines to prostate cancer, as well as the development and evaluation of single and combination therapy modalities for local, regional, and metastatic disease.

The focal point toward which the efforts of the National Prostatic Cancer Project are directed is the prevention and improved treatment of prostatic cancer. This objective is complemented by immediate Project endeavors aimed at decreasing morbidity and increasing survival time of prostate cancer victims.

The widespread use of endocrine therapy for prostatic carcinoma dates back to its first introduction in the early 1940's and continues to result in objective and subjective responses in the majority of patients. However, since hormonal therapy was unable to cure metastatic disease, the desirability of studying drugs which may affect this type of cancer was recognized and led to the July 1973 initiation of the Cooperative Clinical Trials Program of the National Prostatic Cancer Project. This was the first national clinical cooperative program on chemotherapy of prostate cancer with criteria of patient randomization and clinical response tailored to the biological characteristics, metastatic behavior, and age of patients with this disease. Beginning with randomized studies of the effects of single chemotherapeutic agents on patients who fail to respond or no longer respond to conventional treatment, the program has expanded to include clinical trials using both single agents and combinations of agents aimed at patients with metastatic disease who are stable after previous treatment or who are previously untreated. Trials have also been initiated to determine the efficacy of chemotherapy as adjuvants to surgery or definitive radiotherapy in patients with earlier stages of the disease. The National Project also supports radiotherapy studies comparing extended field treatment with local field treatment. Control trials directed at determining the specific efficacy of radiotherapy are near completion. Finally, the National Prostatic Cancer Project supports efforts in the treatment category that are directed towards

the synthesis of compounds with specific prostate cytotoxicity. Agents with potential activity are screened in animal, cell, and organ culture test systems, which are useful in selection of those chemotherapeutic agents for use in Phase I and II trials.

In the detection and diagnosis category, a major effort continues to be directed at developing and testing specific and sensitive immunochemical assays for prostatic acid phosphatase as diagnostic tools. Identification and development of other potentially useful biological markers including polyamines, hormone receptor profiles, the BB isoenzyme of creatine kinase, and cancer indices of various enzyme profiles in serum and prostate fluid are being tested. This work is supported by tissue and serum repositories which provide investigators ready access to cell cultures, tissue samples, and sera samples from men with normal, benign hypertrophic, and carcinomatous prostates. Additional studies are supported through the distribution, by the National Prostatic Cancer Project, of the Dunning R3327 rat tumor model of human prostatic adenocarcinoma.

The search for factors associated with prostate cancer and a better understanding of the nature and history of the disease continues. Ongoing and new projects in the Etiology and Prevention category are directed at further characterization of established animal tumor models (Dunning and Pollard rat tumors) and development of new animal models (Noble tumor). Complementing the in vivo model systems are in vitro organ and cell culture studies of human prostate tissue. The relating of prostatic carcinoma specific antigens to immune mechanisms continues. To date, virologic studies of prostate cancer have shown that viral particles do not play a significant oncogenic role in human prostate cancer. Animals and in vitro models of prostate cancer are being studied extensively for risk factors associated with the development of the disease, and epidemiologic studies are probing the relation of genealogic, dietary, occupational, socioeconomic, sexual, and medical factors to human prostate cancer.

Accomplishments

Significant progress has been made during the past year in the development and further testing of biological markers in the diagnosis and treatment of prostate cancer. A solid-phase immunofluorescence assay (SPIF) previously developed for serum prostatic acid phosphatase (PAP) has been evaluated in 133 patients with various stages of prostatic cancer (Lee, et al, 1980a). The data reveal that an abnormal circulating PAP is obtained in patients with localized and nonmetastatic disease as confirmed by surgical staging and careful inspection of all pelvic lymph node material. This finding may alter current concepts on the staging and/or on the therapy of prostate cancer. A new solid-phase immunoadsorbent (SPIA) assay for PAP has also been developed. The principle of SPIA is similar to that of SPIF, but with two major advantages: PAP can be quantitated against a primary standard thus providing a uniform calibration of the assay, and a single spectrophotometer is required instead of a spectrophotofluorometer (Lee, et al, 1980b). Other immunochemical studies of PAP (Choe, et al, 1979) have shown that it is an antigenically specific marker enzyme for human prostatic epithelial cells.

Purified PAP has been dissociated into subunits and the subunit polypeptides have been further cleaved into peptide fragments and characterized for their amino acid composition, Molecular Weight antigenicity, and catalytic activity. For the antigenic definition of PAP, antibodies to PAP, subunit and lysosomal acid phosphatase from human fibroblasts have been prepared and the antigenicity of PAP-subunit and peptide fragments was studied by RIA and IEA (immuno-enzyme assay). Furthermore, monoclonal anti-PAP antibodies have been prepared and antigenic specificity of PAP has been investigated. Thus far anti-PAP antibodies do not cross-react with fibroblastic lysosomal acid phosphatase and the antilysosomal acid phosphatase (fibroblast) does not cross-react with PAP.

NPCP investigators are also attempting to develop monoclonal antibodies using the lymphocyte hybridoma technique as an approach to detect and define prostate tumor-specific antigens (Wright, 1980a,b). The hybridoma technique circumvents many of the problems associated with xenogeneic immunizations since the monoclonal antibodies represent a single population of antibody-combining sites, and therefore, the potential in obtaining truly monospecific antibodies is great. The procedure used is to prepare single spleen cell preparations from spleens removed from Balb/c mice which have been immunized with DU145 prostate tumor cells. The spleen cells are fused with a mouse myeloma cell line (P3x63 Ag8) and plated in 96-well microtiter plates. Those hybrids which demonstrate specificity are cloned and recloned in soft agar. Only when spleen cells were obtained from hyperimmunized mice, were hybrid cultures found to secrete antibodies that demonstrated a marked preference for the immunizing antigen (i.e., DU145 cells). Of 423 cultures tested, one culture (PD96) produced antibodies with a two-to eleven-fold higher binding activity against DU145 cells than against other malignant and normal cells. The cross reactivity still evident with this line and other lines may diminish upon further cloning. Results to date suggest that the hybridoma technique may be valuable in obtaining monospecific antibodies for the detection and characterization of prostatic carcinoma-specific antigens.

The BB isoenzyme of creatine kinase has been identified in the serum of patients with prostatic carcinoma, and work toward defining the sensitivity and specificity of the isoenzyme as a tumor-associated marker is in progress (Silverman, et al, 1979). Creatine kinase BB is frequently found in the serum of patients with untreated malignancy (80-85 percent). Additional studies involve the identification of antibodies to creatine kinase BB in various types of patients including those with: Stage D prostate cancer in relapse, postsurgery patients with prostatic carcinoma following implantation of a radioactive source, and some patients with benign prostatic hyperplasia (BPH) following surgical resection. The significance of these autoantibodies is being investigated, particularly as a possible source of interference in the radioimmunoassay for creatine kinase BB. Because of the high concentration of creatine kinase BB in prostatic fluid, this isoenzyme is being purified for characterization and use as an antigen in a new radioimmunoassay, with potential improvement in sensitivity and specificity. This work may also elucidate the metabolic pathway catalyzed by creatine kinase BB in prostatic epithelium and/or its secretions.

Other studies of prostatic fluid are in progress because it is thought to represent an adequate sample of the metabolic state of the prostatic epithelial cells and because the evidence suggests that a diffuse identifiable change in metabolic activity precedes or accompanies the development of local carcinoma (Grayhack, et al, 1980). To date, approximately 3600 determinations of lactate dehydrogenase (LDH) isoenzymes have been performed. The ratio of LDHV/LDHI has exceeded 2 in 59 of 70 patients with histologically confirmed carcinoma of the prostate. On the other hand, in 120 out of 140 patients with histologically confirmed BPH without inflammation, the ratio of LDHV/LDHI in their prostatic fluid was less than two. However, the determination of LDH isoenzymes in the prostatic fluid remains nonspecific for identification of patients with a high risk to carcinoma of the prostate since the fluid from patients with evidence of prostatic inflammation also has a high LDHV/LDHI ratio. Other studies have shown that measurement of the C_3 complement and transferrin in prostate fluid has a high probability of distinguishing patients with malignant diseases of the prostate from those suffering with inflamation and benign neoplasia.

Many of the NPCP grant-supported investigations utilize the Dunning R3327 transplantable rat prostate adenocarcinoma. This is one of several useful animal models for prostate cancer that the NPCP has identified. F_1 Copenhagen X Fischer male rats bearing the R3327 hormone-responsive prostatic adenocarcinoma are available at no cost, through the NPCP, to investigators interested in pursuing studies with this tumor model. Some of these animals have been used in studies of hormonal manipulation and irradiation as treatments in the management of prostatic carcinoma. The R3327-H tumor has been shown to contain both estrogen and progestin receptors following castration but not before castration (Heston, et al, 1979) suggesting that this may represent the appearance of a cell population with a "functional estrogen receptor" which would be treatable with antiestrogens. The antiestrogen, tamoxifen (250 $\mu g/kg$/day), has not been effective in suppressing tumor growth to the level of castrate controls, and thus the role of estrogen in the growth regulation of this tumor appears to differ from other tissues such as breast, which also possess receptors for estrogen. To further characterize this tumor, it is being grown in animals which are receiving estrogen to determine if a tumor population can be selected which is estrogen-responsive but not androgen-responsive in growth. The cells of the tumor which are reproductively active are referred to as the clonogenic cell population, and a clonogenic cell assay for the anaplastic variant of the R3327-H tumor, designated R3327-AT has been reported. The effects of prior *in vivo* and *in vitro* irradiation are being determined by use of the clonogenic assay. Other work has shown that the anaplastic variant R3327-AT may represent a model for poorly differentiated carcinoma. It is anaplastic in appearance histologically, it grows rapidly, and it grows equally well in male and female rats. Because of this equal rate of growth in male and female rats, it was believed that it is a hormone-independent tumor. However, when doses of diethylstilbestrol equivalent to the doses of androgen normally used (10mg/kg) are administered, a suppression of tumor growth is noted. At the same time, however, the amount of ^{3}H-thymidine incorporated into tumor DNA is significantly increased. Additionally, it appears that steroids may alter the potential of these tumor lines to metastasize, and tumor lines for their differential metastatic ability are now being selected.

The R3327 has also been used to investigate the immunologic aspects of prostatic cancer (Lubaroff, et al, 1979). A variety of standard immunization techniques have been used to induce antibody and cell-mediated responses to the antigens associated with this tumor. Cellular-immune responses to major and minor histocompatibility antigens as well as tumor antigens have been detected using in vivo (rejection of growing tumor and protection against tumor challenge) and in vivo (cell-mediated lympholysis and mixed-lymphocyte tumor interaction) assays. Antibody responses to many antigens associated with the R3327 tumor have also been detected, and these include species, organ, as well as major and minor histocompatibility antigens. Earlier in vivo experiments showing enhanced tumor growth in immunized rats as compared to unimmunized rats would indicate the possible presence of blocking antibodies directed against the tumor. The R3327 tumors growing in recipient Copenhagen rats can be destroyed by treatment with cryosurgery (Bonney, et al, 1978). This destruction is dependent upon tumor size, in that tumors smaller than $1000mm^3$ are completely destroyed whereas those larger than $1000mm^3$ cannot be destroyed. In recent experiments, attempts have been made to determine whether the immunotherapeutic agent, BCG, would enhance the effect of cryosurgery. In addition, investigations have been initiated to determine whether cryosurgery with or without BCG would induce protective immune responses to the R3327 tumor. Data obtained thus far indicate that the combination of BCG and cryosurgery is better in reducing or eliminating tumor than cryosurgery alone, particularly when treating large tumors. In general, small tumors are controlled equally as well by BCG plus cryosurgery or cryosurgery alone. BCG alone is ineffective in all cases. Also, initial results would indicate a protective immunity produced against the R3327 tumors by the combination treatment of BCG and cryosurgery.

Two other animal models for studies of prostate cancer have been previously described in NPCP Annual Reports. Three tumor cell lines have been shown to have predictable patterns of metastases and the organotropism of each cell line is also reproducible (Pollard, 1979). This model offers the means to examine the characteristics of prostate tumor cells, possible etiological agents or mechanisms, responses to manipulations which modify their multiplication, their metastatic patterns, and organotropisms. For example, administration of sodium barbiturate (0.1 percent) in the drinking water accelerates the rates of tumor spread, while orally administered indomethacin (a prostaglandin inhibitor) reduces the rate of spread. An in vitro cell colony inhibition test has been developed which has been used to further analyze the mechanisms of metastasis. It appears to be related to circulating very low-density lipoprotein (VLDL) in the serum. VLDL is a stable oncolytic agent whose role in oncogenesis and in metastasis is under investigation. Rats with line III tumor cells were inoculated intravenously with small doses of heparin at daily intervals. The rate of tumor metastasis was accelerated, and this was accompanied by a reduction of VLDL in the circulating blood. A VLDL inactivating factor, probably lipase, appeared in the serums of rats at 10 minutes following i.v. inoculation of heparin into normal rats (Chan and Pollard, 1980).

The Noble (Nb) animal model of prostatic adenocarcinoma has also been described previously. This model has been used mainly to study chemotherapeutic and hormonal treatments of prostate cancer. Using androgen-dependent and autonomous

tumors, multiple experiments have been carried out to evaluate the response to chemotherapeutic agents including, cyclophosphamide, 5-fluorouracil, adriamycin, methotrexate, cis-platinum, DTIC, and BCNU. Cyclophosphamide and adriamycin to date have been the most efficacious agents in terms of not only decreasing tumor growth rates, but also in decreasing the number of metastases present in animals so treated (Drago, et al, 1979a,b). Additionally, the androgen-dependent tumors have been subjected to various hormonal manipulations at varying tumor sizes, and hormonal manipulation even at a large tumor size, has been shown to be efficacious in reducing tumor size. However, if castration is carried out when the tumor volume is small, tumor growth is markedly reduced, but does not completely disappear with this modality alone. Currently, combination of hormonal manipulation, either castration or estrogen administration, plus chemotherapy is being pursued. This early combination chemotherapy with hormonal manipulation in the androgen-dependent tumors may be of importance in addressing the question of whether or not the tumor growth rates are affected with early chemotherapy more than with castration alone.

Studies of primary outgrowth from prostatic tissue are being carried out in an effort to define a simple, reliable, and reproducible method of culturing TUR specimens. This would permit growth of cells from a patient for the purpose of testing therapeutic modalities and for prognostic purposes (Clarke and Merchant, 1980). Tissue for culture has been obtained from 176 patients. Outgrowth was obtained from 61 specimens with 46 (75 percent) yielding only epithelial cells, 5 (8 percent) yielding only fibroblasts, and the remainder yielding both epithelium and fibroblasts. One hundred percent of fragments which contain glandular tissue will adhere in culture and give rise to epithelial outgrowth. Every instance of failure can be related to damage from the surgical procedure or lack of glandular tissue.

Tissue cultures and explants of human prostate have been used effectively to examine ultrastructural and biochemical events associated with the transformation of normal prostate tissue with chemical carcinogens and in studies of the effects of modulation of vitamin A and hormones or carcinogenesis (Heatfield, et al, 1979). In addition, induction of aryl hydrocarbon hydroxylase (AHH) of the microsomal mixed function oxidase system has been studied in explant cultures of normal human prostate exposed to benzanthracene (BA). Induction of AHH in a given tissue is a measure of the capacity of that tissue to metabolize certain inactive polycyclic aromatic hydrocarbons, such as BA, to their carcinogenic forms. In these studies, AHH activity was measured by a fluorometric method using 3-hydroxybenzol-alpyrene as a standard (Kahng et al, 1980). In four surgical specimens (BPH-TUR) studied, AHH induction, expressed as induction ratios (AHH in BA-treated/control tissue), showed considerable individual variation, ranging from 12-to 163-fold. In the one specimen of adenocarcinoma studied so far, AHH induction was not observed when exposed to BA *in vitro*. This may indicate loss of enzyme induction following cellular transformation. AHH induction also was measured in cell cultures. Induction of AHH in epithelial cell cultures was studied following exposure to BA, 9, 10-dimethyl 1, 2-benzanthracene (DMBA), or N-methyl-N'-nitro-N-nitrosoguandine (MNNG). MNNG, a direct acting carcinogen, had no effect on AHH induction. Cells treated with MNNG showed the same AHH activity as controls. This observation is consistent with the fact that MNNG does not require metabolic activation by the mixed function oxidase system (MFOS). On the other hand,

carcinogenic polycyclic aromatic hydrocarbons such as BA and DMBA, which require metabolic activation, cause an induction of AHH activity up to 80-fold in the case of DMBA. So far, these investigators have demonstrated that prostatic epithelial cells (basal cell derivatives) do respond to the carcinogen treatment resulting in induction of AHH, and this response is specific for different classes of carcinogens. The wide range of AHH induction values indicates a wide inter-individual variability of human tissues in response to a carcinogen challenge.

Biochemical determination of whether steroid hormone receptor measurements on prostate tissue will have clinical applications in diagnosing and selecting optimal therapy for prostate cancer patients continues to be under extensive investigation. A new approach to this field utilizes fluorescence microscopy. More than 350 specimens of human prostate have been assayed histochemically for both estrogen (ER) and androgen (AR) receptors. The percentage of ER and/or AR positive prostatic carcinomas studied to date was 73 percent. This figure is close to the percentage of patients with this disease who respond to the hormonal therapies. These results suggest that histochemical methods for the detection of steroid hormone receptors will provide a simple, rapid, and inexpensive assay for predicting hormone sensitivity of prostate cancers (Pertschuk, et al, 1980).

Noninvasive methods have also been evaluated for diagnosing prostate cancer including ultrasonography. A total of 789 transrectal ultrasonic scans have been performed on 719 patients. Patients evaluated included: those presenting with symptoms of bladder outlet obstruction, patients referred for evaluation of prostatic nodules detected on rectal examination, patients with newly diagnosed prostatic malignancies being considered for radical prostatectomy, and patients with prostatic malignancies being treated with hormonal manipulation or chemotherapy. The studies to date suggest both the limitations and benefits of transrectal ultrasonography in the evaluation of prostatic malignancy. Patients with clinically unsuspected carcinoma can be diagnosed by ultrasonic studies; however, false negative studies do occur as evidenced by carcinoma in tissue removed at time of simple prostatectomy. With presently available instrumentation, it is difficult ultrasonically to differentiate between prostatitis, carcinoma, and calculi. Prostatic ultrasonic scanning is an accurate means of properly staging prostatic malignancies and is useful in detecting tumor regression following hormonal treatment or radiation therapy; its value in detecting early tumor reactivation remains questionable. Finally ultrasonography has some potential as an objective means of measuring tumor response following institution of specific cytotoxic chemotherapeutic agents (Resnick, et al, 1980).

The clinical trials program of the National Prostatic Cancer Project has completed six randomized Phase II studies of chemotherapeutic agents in patients with histologically proven advanced Stage D cancer of the prostate. These trials have demonstrated that patients who have become failures to hormonal therapy may still benefit from systemic therapy in the form of single antineoplastic agents. Therefore, current trials have been designed to determine which of these agents is most effective in this regard when used singly or in combination with other antineoplastic agents or hormonal agents in both patients with advanced disease who have become failures to hormonal therapy,

and those with a smaller tumor load who have newly diagnosed Stage D disease, or stable Stage D disease who are being treated with hormonal therapy. The most commonly used therapeutic approach for patients with newly diagnosed Stage D disease has traditionally been either DES therapy or orchiectomy. These therapies are now being compared with DES plus cytoxan and with cytoxan plus estracyt. In the stable Stage D patients, DES alone is being compared with DES plus cytoxan and DES plus estracyt. Two long-term adjuvant studies are also under way to examine the use of cytoxan and of estracyt to prevent reoccurrence in patients who have received a definitive prostatectomy or definitive irradiation externally or internally. To date, over 1400 patients have been randomized to 12 chemotherapy protocol studies in 11 participating institutions throughout the United States. The different protocols are designed to evaluate single and combined chemotherapeutic agents in patients with histologically proven metastatic (Stage D) prostatic cancer as well as in adjuvant studies for patients with earlier disease (Stage B_2-D_1). The protocols for advanced Stage D disease are further divided to consider patients who have had prior extensive radiotherapy and cannot be treated with myelosuppressive agents. Based on objective response criteria, 5-FU, cytoxan, prednimustine, estracyt, and DTIC have shown activity and responders have experienced markedly increased survival time (Slack, et al, 1980). The results of the National Prostatic Cancer Project Clinical Trials Program to date have been summarized by Schmidt, J. D., et al, (1980).

Other Program Activities

A Prostate Cancer Tissue Collection Center is supported by the project in order to provide investigators with normal, benign hyperplastic, or neoplastic human prostate specimens. Patient histories are available for all specimens in the repository. Prostatic cell cultures and samples of prostate tissue preserved in nutrient media frozen are also available to investigators. From the beginning of the Program in 1974 through December 1979, shipments of these materials have been distributed to 45 laboratories throughout the United States, Canada, and Europe.

The NPCP has also established a serum bank of over 5500 specimens from patients with prostatic cancer. The serum samples, individual and serial, along with patient clinical information are available to qualified investigators for research relative to prostatic cancer. These samples have been used in the development and testing of creatine kinase BB as a diagnostic serum marker for prostate cancer, the establishment of the utility of monitoring sex hormone-binding globulin levels in patients in order to determine the efficacy of certain hormonal therapies, identification of viral antigens, and testing of a cancer serum index for prostate cancer.

Emphases and Projections

The National Prostatic Cancer Project continues to investigate and implement programs and strategies for experimental and clinical research which, based on the evaluation and anlysis of current knowledge and information, will offer the best opportunities for immediate and visible success at all levels of endeavor.

In the Etiology/Prevention area, studies will focus on experimental biology and epidemiology of prostate cancer. In vitro research utilizing animal and human tissues, appropriate in vivo studies, and investigations of etiologic factors associated with prostate cancer are being emphasized. Areas of priority are:

analysis of prostic fluid for determination of acinar cell milieu and the detection of biological markers;

identification of risk factors and prevention approaches in populations with differing risks of prostatic cancer;

trace metals in prostatic cancer;

cytogenetic factors in prostate cancer;

further characterization of hormone receptors in normal, BPH, and cancerous prostatic tissue;

role of intrinsic factors in prostatic carcinogenesis;

endocrine alteration associated with the development of prostatic cancer;

environmental factors which may determine the development of prostatic cancer;

role of peptide hormones in growth regulation of normal and malignant prostatic epithelium; and

growth and maintenance of normal, benign, and malignant human prostatic epithelium in vitro.

In the Detection/Diagnosis area, studies dealing with earlier detection and more accurate diagnosis of the stage (clinical and pathological) of prostate cancer, and the response to therapy are being emphasized. Priority areas for the upcoming year are:

the surface of normal and malignant prostatic cells;

immunoregulation in prostatic cancer;

biochemical markers for detection and evaluation of response to therapy in patients with prostatic cancer;

evaluation of noninvasive physical techniques for the detection of prostatic adenocarcinoma;

morphologic definition of lesions associated with and precursor to adenocarcinoma of the prostate;

interaction between stroma and epithelium of the normal and

neoplastic prostate gland;

evaluation of the use of histochemical techniques for the localization of androgen-binding proteins in the prostate gland;

comparison of analytical methods of prostate cancer detection;

genetic studies in prostatic cancer;

HLA markers in prostatic cancer; and

cytogenetic analysis of prostate cancer.

In the treatment area, the National Prostatic Cancer Project has defined among its objectives (1) the evaluation and improvement of additional therapy modalities on prostatic cancer by synthesis, testing, and selection of new agents and procedures, and the determination of their therapeutic effectiveness, and (2) the development of combination therapeutic modalities where appropriate, based upon new information, and the evaluation of their usefulness in clinical disease states involving local, regional, and metastatic disease. Emphasis continues to be placed on:

studies of cytotoxic chemotherapy agents for prostate cancer;

extent of radiation field and role of adjuvant chemotherapy in patients with node-positive prostatic cancer;

evaluation of nutritional status and nutritional intervention in advanced prostatic cancer;

development of radioisotope agents for detection of metastatic disease (staging) and for therapy of advanced cancer of the prostate; and

prognostic tests and evaluation of treatment modalities for human and animal prostatic cancer.

Phase II trials will be continued to determine the efficacy of single and combination treatments of hormone and antitumor agents in patients with advanced disease, and Phase III trials using adjuvant chemotherapy against early stages of prostate cancer.

NATIONAL PROSTATIC CANCER PROJECT

(Dollars in Thousands)

NONCOMPETING		COMPETING		TOTAL	
NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
34	$3,469	11	$1,261	45	$4,730

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CLINICAL CANCER EDUCATION PROGRAM

Description

Since 1948 the National Cancer Institute has encouraged improvements in the quality of education relative to cancer provided to physicians and dentists, the two health professions most concerned with the diagnosis and management of malignant diseases. Medical and dental schools were eligible to apply for grants to achieve a "coordination" of cancer teaching and to provide additional experiences for undergraduate students to expand their understanding of cancer in its basic and clinical aspects. In 1966, this grant program was revised to include stipends for graduate trainees in clinical oncology in appropriate specialties, and to promote educational activities relative to cancer for practicing physicians and dentists. In addition to medical and dental schools, schools of public health, cancer institutes, and major teaching hospitals affiliated with medical schools became eligible for these grants.

In 1974, following a general phase-out imposed on all training programs at the National Institutes of Health, a new program known as the Clinical Cancer Education Program was initiated to carry forward the objectives of the earlier programs, namely, to stimulate and expand multidisciplinary efforts in cancer education at the undergraduate, graduate, and continuing education levels so that physicians and dentists might deal most effectively with the clinical aspects of cancer. This new program, as did its predecessors, provides support by means of grants for selected faculty and staff, teaching equipment and supplies, consultants, and travel, but supports no trainees. However, undergraduate and graduate students may receive salaries for portions of time devoted to cancer educational experiences. A 15-member Clinical Cancer Education Committee reviews applications for these grants, visits applicant institutions, and advises on program needs and accomplishments. The major teaching activities supported by means of these grants include curricular reviews and analyses, development of core-curricula on cancer, cancer courses, establishment or expansion of multidisciplinary cancer teaching experiences such as conferences, seminars, clinical rotations, and electives, the development of teaching materials and aids, exposure to visiting consultants and to specialized cancer facilities, and periods of intensified education relative to cancer of varying duration. All of the activities for which support is provided must be multidisciplinary and all must be evaluated for their efficacy.

In 1979, awards were made to 98 institutions. Sixty-two of these awards were noncompeting continuations and 36 were new or renewal applications. The budget for fiscal year 1980 ($10,904,000) permitted awards to 79 ongoing and an estimated 18 new or renewed applications.

Accomplishments

Unlike research projects, the outcome of cancer education programs cannot be judged by the contributions published by grantees in scientific journals.

Improvements in the scope and quality of cancer instruction, in the extent of multidisciplinary cancer teaching activities, in the numbers of undergraduate and graduate students seeking specialized periods of cancer instruction, and in the numbers of practitioners responding to educational offerings are described by all grantees in their progress reports. It can be assumed that these activities lead to improvements in the quality of care provided to cancer patients by students and practitioners who benefit from these experiences. Site visitors to applicant institutions have been impressed with the extent to which the goals of the earlier programs have been achieved.

The Clinical Cancer Education Committee has reviewed 32 applications during three meetings for July 1, 1980 funding, and has visited 28 institutions. Progress reports received from 65 institutions were reviewed by members of the Clinical Cancer Education Committee at their meeting on November 7, 1979. Additional information was secured for clarification and queries resolved. All reports were considered satisfactory. The review of progress reports on 83 current grantees was completed by the Clinical Cancer Education Committee at their meeting in June 1980; the balance were reviewed as part of renewal applications.

A workshop on Physician Education in Cancer Nutrition was held on June 4-5, 1979 to examine the scope and content of physician education in diet and nutrition as they relate to all aspects of cancer, and to determine their adequacy and also the best possible methods of providing necessary education in this subject to undergraduate medical students, residents, fellows in graduate specialty training programs, and medical practitioners. Proceedings of this workshop have been published in the Journal of Cancer Nutrition.

Emphases and Projections

A workscope was designed for a contract which was awarded in September 1979 to develop an appropriate and valid method for the evaluation of cancer education activities which are carried out at institutions receiving the Clinical Cancer Education grants. The objectives of the current grant guidelines will be redefined, a sample of the grant applications and progress reports will be reviewed, and a system of monitoring and data analysis will be designed which would enable assessment of the individual components of each program, and their variations over a period of time.

The success of the recent workshops on graduate education in the medical specialties and related educational needs indicates a need for additional programs in other disciplines. However, uncertainty regarding the status of this Program following the proposed reorganization has delayed plans for new workshops.

Other Program Activities

Coordination is maintained with the Training Branch, National Cancer Institute, with the Division of Cancer Control and Rehabilitation, National Cancer Institute, and to a lesser extent with the Office of

Cancer Communications, National Cancer Institute. Participation is maintained in the activities of the American Association for Cancer Education. Consultants to the Program include, in addition to the members of the Clinical Cancer Education Committee, numerous clinical oncologists throughout the country who are experts in cancer education; 16 such individuals have provided services to this Program in the past year.

CLINICAL EDUCATION

(DOLLARS IN THOUSANDS)

NONCOMPETING		COMPETING		TOTAL	
NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
79	$ 9,263	18	$ 1,641	97	$10,904

Description

The Research Manpower Branch supports research training in scientific specialties composing the broad areas of cancer etiology and prevention, cancer detection and diagnosis, and cancer treatment and restorative care. The training may be in clinical or nonclinical specialties and may be in either basic or applied research. Three grant mechanisms are used to support research training, namely:

a) the Institutional Fellowship Award;
b) the Individual Fellowship Award; and
c) the Research Career Development Award.

The first two of these awards were created in 1975 by the National Research Service Act. Institutional awards are made competitively to qualified institutions to develop or enhance research training opportunities at the predoctoral and postdoctoral level. The applicant must have the staff and facilities for the proposed program. After the award is made, the institution's training program director is responsible for selecting the trainees and for administering the program. Residencies may not be supported by this program.

Individual fellowships are awarded only for postdoctoral research training in nonprofit institutions here and abroad. An applicant for a postdoctoral fellowship must establish his acceptance by a preceptor and must present a detailed description of the research project which he will undertake as part of his research training. Residencies may not be supported by this program.

Research career development awards are not governed by the National Research Service Act. The purpose of these awards is to provide very promising young investigators the opportunity to devote full time to their development as competent, independent cancer investigators. Applicants must demonstrate appropriate scientific experience and achievement and must have outstanding research potential.

Accomplishments

During the year 1,519 trainees and fellows and 111 research career development awardees were supported. Their distribution in the three broad research training areas was as follows:

Institutional Fellowship Awards
(training grants)

	Predoctoral	Postdoctoral
Cancer Etiology and Prevention	468	533
Cancer Detection and Diagnosis	61	67
Cancer Treatment and Restorative Care	22	154

Individual Postdoctoral Fellowships

Cancer Etiology and Prevention	149
Cancer Detection and Diagnosis	6
Cancer Treatment and Resorative Care	59

Research Career Development Awards

Cancer Etiology and Prevention	76
Cancer Detection and Diagnosis	9
Cancer Treatment and Restorative Care	26

In July 1980 two Workshops on the Pathobiology of Cancer will be held in Keystone, Colorado and Lake Placid, New York. Both courses will accommodate approximately 90 NCI research trainees and fellows who lack previous training in the actual disease mechanisms of cancer.

Some of the notable research accomplishments in the past year by postdoctoral fellows, trainees, and research career development awardees include the following:

Dr. Patricia L. Marion, an NRSA Postdoctoral Fellow, has studied hepatitis B virus (HBV) and hepatocellular carcinoma. She has found that the HBsAg antigen produced by primary hepatocellular carcinoma cells is identical to the HBsAg particles found in the serum of infected patients. The HBV-specific DNA within the cells was found to be integrated into the cellular DNA in at least three sites, with all or nearly all of the HBV genome present and transcribed.

Dr. Dennis D. Cunningham, a Research Career Development awardee, has studied a cell-surface component involved in thrombin-stimulated cell division. He has found that thrombin can stimulate cell division by acting at the cell surface, and that it need not be internalized in order to bring about its biological effects. A thrombin-specific receptor has been identified, and it has been shown that thrombin must bind to and cleave this receptor in order to stimulate cell division.

Frank R. Jones, an NRSA trainee, has developed an effective immunotherapy for feline leukemia in which IgG and circulating immune complexes are removed from feline plasma by means of an ex vivo immunosorbent. The cats responded to treatment by a dramatic reduction of circulating lymphoblasts and of lymphadenopathy, and by a gain in body weight. Moreover, they reverted to the feline leukemia virus negative state and exhibited markedly increased survival time.

Margo N. Woods, an NRSA postdoctoral fellow, studied the effect of fiber on intestinal microorganisms, drug absorption, and metabolism. She found that bran consumption did not alter the steady state levels of digoxin. Fecal excretion of metronidazole was enhanced in germ-free rats on a high bran diet, whereas both fiber and bacteria appear to decrease the speed and amount of urinary excretion of metronidazole.

Argyrios N. Theofilopoulos, a Research Career Development Awardee, has studied the association of immune complexes with cancer and with various immunologic disorders. He has found that measurement of immune complexes is useful in diagnosis, prognosis, and management of patients with malignant and nonmalignant diseases, and has developed a sensitive and specific immunoassay for this purpose.

Dr. E. Carmack Holmes has studied the immune response in patients with lung cancer. He has found that BCG immunotherapy is effective in Stage I of patients with lung cancer. Levamisole, Thymocin, and other agents are now being considered for use in later stages of lung cancer. Dr. Holmes has indicated that the immunotherapy should be combined with either surgery, radiation therapy, or chemotherapy.

Emphases and Projections

Twenty-nine applications were received and reviewed in the new Veterinary Pathology Residency Training Program. Of that number, 26 were approved. Ten had technical merit scores better than 218 and were funded. They will support 40 new trainees annually in an area of extreme manpower shortage.

A second cancer pathobiology course was initiated this year to accommodate the increasing demand by NCI trainees. Even with the additional course, more than 100 trainees and fellows had to be denied this training.

To combat the shortage of physician-investigators, this Branch is considering beginning a "Clinical Investigator Award Program," which would offer qualified physicians an opportunity to fully develop their skills as researchers.

Research Manpower Branch
(Dollars in Thousands)

Institutional Fellowships

Noncompeting		Competing		Total	
No.	Amount	No.	Amount	No.	Amount
94	$ 11,000	63	$ 12,047	157	$ 23,047

Individual Fellowships

Noncompeting		Competing		Total	
No.	Amount	No.	Amount	No.	Amount
120	$ 2,143	100	$ 1,924	220	$ 4,067

Research Career Development Awards

Noncompeting		Competing		Total	
No.	Amount	No.	Amount	No.	Amount
83	$ 3,108	29	$ 1,015	112	$ 4,123

Research Career Awards

Noncompeting		Competing		Total	
No.	Amount	No.	Amount	No.	Amount
5	$ 160	0	0	5	$ 160

Description

The Cancer Research Facilities Program was initiated in September 1971 with a public announcement of the availability of grant funds to create additional cancer research facilities. The essence of this announcement is set forth in the following paragraph:

> In accordance with the President's call for an expanded, intensified, and coordinated cancer research program, and under authority provided by the Congress in the fiscal year 1972 appropriation act, the National Cancer Institute initiated a program of grant-supported construction of cancer research facilities. The intent of this program is to create new physical resources for cancer research through Federal participation in the cost of new construction and renovation. Support may be provided for the construction of facilities such as basic research laboratories; clinical research facilities; animal facilities; and basic associated core, administrative, laboratory, and service space. In all instances, the facilities proposed must be intended for expansion of cancer research for at least 20 years. A purpose of this program, in addition to strengthening research capabilities at existing cancer centers, is to develop new strong multidisciplinary cancer efforts in regions of the country where they do not exist. Thus, in the consideration of applications some attention will be given to geographical distribution as well as to the relation of proposed construction for existing centers of excellent cancer research.

Justification of construction funds has been, and will continue to be, in terms of new cancer research programs and in the provision of safe facilities for accomplishing biohazardous cancer research. The primary review and evaluation of applications have been essentially scientific, considering such matters as scientific merit of the proposed program(s), the technical competence of the applicant institution staff, the intellectual environment of the applicant institution, and its scientific, fiscal, and administrative capabilities. In addition, other criteria have been considered, such as the location of the applicant institution, the applicant institution's role in the National Cancer Program, the promptness with which construction can be started, space requested commensurate with projected program scope, essential minimal facilities for those institutions with an undeveloped cancer research program, net space utilization of 60 percent or more, reasonable cost per gross square foot, and acceptable design criteria.

During fiscal year 1980, 12 construction grant applications requesting $19,842,551 were received and 11 were reviewed by the site visit teams; one was reviewed by the Program Director as an administrative supplement. Following the site visits, parent review committees held additional deliberations. After the final evaluation by the National Cancer Advisory

Board, 9 applications were recommended for payment in a total amount of $12,231,187.

Additionally, a carryover obligation (from fiscal year 1979) on 2 grants totalled $1,867,323. Thus, the NCI Construction Program faced approved funding requests of $14,098,510 after the initial evaluation of fiscal year 1980 applications.

The Construction Program's fiscal year 1980 budget was $11 million. These funds were awarded for the following projects:

- Completion of two previous (fiscal year 1979) awards:
  St. Jude Children's Research Hospital (1 C06 CA25869-01)
  University of California, San Diego (1 C06 CA25814-01)

- New awards for biohazard containment facilities:
  Cornell University (1 C06 CA28152-01)
  Harvard University (1 C06 CA28144-01)
  Fred Hutchinson Cancer Research Center (1 C06 CA23718-01A1)
  Johns Hopkins University (1 C06 CA26698-01)
  Michigan Cancer Foundation (3 C06 CA21123-01A2S1)
  Ohio State University (1 C06 CA28132-01)
  Roswell Park Memorial Institute (1 C06 CA28150-01)
  University of Minnesota (1 C06 CA28136-01).

One application, University of Arizona (1 C06 CA28195-01), was approved and recommended for funding but was not funded due to lack of program funds. The recommended funding for this application was $1,396,154.

A major accomplishment was the completion of "An Analysis of Construction Data of the NCI Construction Program, 1972-1979." It was requested by the National Cancer Advisory Board's Subcommittee on Construction.

Overview of Branch Activities

The Research Analysis and Evaluation Branch (RAEB) serves as a major source of scientific information on NCI-supported research projects. Members of the Branch analyze and index the scientific content of all grants awarded by NCI, all NCI contracts, and all NCI intramural projects, and keep track of published results supported by grants through a literature surveillance program. This information is disseminated throughout NCI--to the other Divisions, Office of the Director, Office of Cancer Communications, Financial Management Branch, Program Analysis and Formulation Branch, and the International Cancer Research Data Bank; to other NIH organizations such as the Research Documentation Section and the Research Analysis and Evaluation Branch of the Division of Research Grants; to other NIH Institutes; and to other Government and private organizations. Staff members also compare pending grants and contracts with existing NCI-supported projects at the same institution to assure that there is no overlap or duplicated support.

The number of requests for information continued to be high during the fiscal year, mainly because of the reorganization of the Institute initiated in 1978. DCRRC program directors were transferred to other NCI Divisions, causing a decentralization of personnel and a great increase in the number of staff members responsible for the programmatic aspects of NCI grants. Requests are therefore coming not only from former DCRRC program directors but also from their colleagues in the other Divisions who must familiarize themselves in detail with grant-supported programs. Because the Branch acts as a central source of information, some of the difficulties usually resulting from a decentralization of personnel have been kept at a minimum.

Computer Information System: GENIUS

The heart of the operation of the Research Analysis and Evaluation Branch is the Grants Elements Network-Internal Users System (GENIUS), in use since 1975. The bulk of the data base consists of scientific data for NCI grants indexed according to pertinent terms from a list of fixed terms compiled by the Branch and according to specific key words or phrases taken by the indexer from the text of the grant application. Data can be retrieved in a variety of formats in order to respond to inquiries and prepare reports.

In addition to the scientific indexing prepared by the Branch, two other types of data are available from the system. These include administrative data obtained from the Division of Research Grants' (DRG) IMPAC System and Smithsonian Science Information Exchange (SSIE) abstracts supplied by the applicants and entered into DRG's CRISP System.

When completely operational, the Grants Elements Network-Internal Users System will include data from five separate computer information storage files: (1) active research grants and companion history file of terminated grants, (2) unfunded grants and history file which includes a

total of five previous years of data, (3) active contracts, (4) intramural research projects and history file, and (5) training programs. All scientific and administrative data on the active and history files and the intramural research file, except for the SSIE abstracts, are searchable on the computer. The current unfunded grants file consists of disapproved and approved-but-not-funded grants for the past two years. This file contains only administrative data from IMPAC. The project title, program area, applicant department, and study section are the only points of access to scientific information on these projects.

The intramural research project file was added to the GENIUS system and became operational during fiscal year 1978. It is anticipated that an active contracts file will become operational by the end of this fiscal year and a training file by fiscal year 1981. The major programming efforts in early fiscal year 1980 were directed at expanding the capabilities of the existing systems through addition of more data items (e.g.,adjusting future money from direct costs only to direct plus estimated indirect costs) and more efficient storage and searching of data with the aid of techniques such as variable length records.

About 80 percent of the active grants, including new proposals and type 2 requests for continuing support, and 50 percent of the intramural research projects have been entered into the system. GENIUS is maintained and operated solely by the Branch, which is greatly indebted to the Division of Computer Research and Technology for help in developing and implementing the system. Other Institutes at NIH have expressed interest in GENIUS and, with the help of DCRT, are using it as a model for their own systems.

Last year, staff of the Branch explained and demonstrated the GENIUS system in detail to representatives of Enviro Control, Inc., a contractor chosen to review and compare the science information systems within NCI and NIH in terms of their content, quality, capabilities, and usage. The contractor's staff will characterize a total of eight information systems, examining types of information classification, sources, operating personnel, and retrieval products, as well as user satisfaction. They are now in the process of writing a final report on their findings.

Requests for Information

Requests to the Branch are made daily and vary in complexity. Most are now answered by using the GENIUS system, but other sources of information are maintained and used frequently by the Branch. These include copies of grant applications and contract proposals for active projects, progress reports, study section summary statements, reprints of published grant-supported papers, and documents concerning individual trainees and fellows. The Branch has also developed several unique files of information, including one that lists the names and backgrounds of professional personnel on all grants submitted to NCI. This file is used often by RAEB members and by staff of the Review and Referral Branch looking for and verifying the names of scientists with a particular expertise to send on site visits.

The number of requests for information continued to be high during 1979; Branch members answered about 600 inquiries. Thirty percent came from the Office of Cancer Communications and ranged from answers to letters from the public to inquiries from members of the Congress and White House staff. The remainder came from the NCI Office of the Director (14 percent), other NCI Divisions (31 percent), other NIH organizations (3 percent), and non-NIH organizations and individuals (22 percent). Because of this continued high rate and complexity of requests, much more time and effort had to be spent this year in the information retrieval process, resulting in fewer staff-hours available for scientific indexing of information for input into GENIUS.

Requests covered a wide range of topics, such as the following:

1. Interferon
2. Biological effects of ionizing radiation
3. Biological response modifiers
4. Hyperthermia
5. Chronobiology
6. Asbestos
7. Populations exposed to DES
8. Development of prostheses
9. Marijuana-like drugs to control nausea
10. Hepatitis and its relation to cancer.

Special Projects

This year Branch staff devoted much time to requests to retrieve and analyze information for special programs and activities coordinated in the Office of the Director, NCI. Mr. Harry Canter, Chief of the RAEB, and Ms. Rosemary Cuddy, Deputy Chief, attended a number of meetings dealing with each of these programs and activities and, along with other members of the staff, were directly involved in providing the necessary information.

Diet, Nutrition and Cancer Program

During this year, Branch staff continued to assist the Diet, Nutrition and Cancer Program (DNCP), established to coordinate all nutrition research supported by the various NCI programs. The function of the Nutrition Program is to collect, analyze, and disseminate information on the interrelationships between diet, nutrition, and the etiology of cancer and the therapy and rehabilitation of the cancer patient. Program members initially requested assistance from the Branch about two years ago after studying the information systems in operation at NCI and recognizing that the GENIUS system best met their needs.

The Branch is playing a growing role in helping the DNCP to implement their information function. Branch staff now participate in DNCP meetings, send Program members copies of indexed grants identified as nutrition oriented, keep track of pertinent grants with a special computer code, and answer information requests received by the Program. To answer such requests as efficiently as possible, the Branch keeps a master DNCP project list of all

NCI-supported grant, contract, and intramural nutrition projects, including professional and public education. The RAEB recently made available to the DNCP a monthly listing of current literature resulting from DNCP grants and companion subject index. This list is a subset of the broader literature surveillance program of the Branch.

This year, as well as last, Branch members assembled data for the DNCP Status Report. In April they also answered a lengthy request from the General Accounting Office to determine if nutrition research is getting an adequate share of grant support; the reply was based on data from all grants reviewed during 1978, 1979, and 1980, whether funded or unfunded. To make it easier to develop these types of reports in the future, Branch members now evaluate all NCI-supported grants, contracts, and intramural research to estimate the percentage of dollars spent on each project for nutrition research.

Bellrad Research Projects Analysis Subcommittee

The RAEB is currently providing information expertise to aid NCI and NIH in their role on the PHS Subcommittee to Coordinate Radiation Activities. Mr. Canter and Ms. Cuddy are members of the Biological Effects of Low Level Radiation (Bellrad) Research Projects Analysis Subcommittee, formed at NCI to concentrate on this topic of major concern to the PHS Subcommittee. Branch members are developing a separate file of information on low level ionizing radiation and incorporating into the GENIUS system a special series of radiation-related categories developed by the Bellrad Subcommittee. In this way, the RAEB will be able to store, search, and retrieve information on NCI-supported grant, contract, and intramural research projects according to criteria determined by the Subcommittee and will continually update the data set. They will also incorporate similar information on projects supported by the other NIH Institutes, to be provided by the Division of Research Grants, NIH.

Smoking, Cancer And Health Program

The RAEB is also applying its centralized information system to the Smoking, Cancer and Health Program. Branch members have retrieved information on all NCI-supported grants, contracts, and intramural projects related to this area of research, including studies on bladder and lung cancer, and have sent it to the Director's Office for a decision on their pertinence to the Program. During this year, staff will help develop new categories for coding the projects for this Program.

Literature Surveillance

Published results are monitored through the Branch's literature surveillance program. About 320 major medical and scientific journals are scanned to identify those papers resulting from NCI grant-supported or combined grant- and contract-supported research. These references, and additional references obtained from reprints submitted by grantees, are arranged according to NCI cancer activities and published monthly with a subject and author index as the NCI Grant-Supported Literature Index.

The Index is the most complete record available of accomplishments of the total extramural research grant program and is entered into a computer searchable system. In calendar year 1979, about 7684 articles, representing the work of 14,034 authors, appeared in the Index.

Communications Activities

As part of an NCI-wide effort to improve communications, the Branch Chief has been participating in the Program Working Group on Information Systems/ Communication. This group is primarily concerned with scientific and technical information resources from all NCI Divisions. This year the group helped prepare the biannual inventory of NCI information activities, which is required by the National Cancer Act. RAEB staff identified grants and contracts that contain a communication/information component, obtained projects summaries from GENIUS, and distributed them to division representatives. The inventory should be completed by early summer of 1980.

Staff members also serve on Division and Institute committees that attempt to foster better communications about NCI-sponsored research in areas judged especially significant to the National Cancer Program. One such committee is the Office of Cancer Communications' Ad Hoc Group on Cancer Information Clearinghouse Operations.

The Branch maintains regular liaison with other Divisions of NCI. Extra copies of grantees' reprints are sent to each Division, as are copies of the SSIE abstracts for all grants. SSIE abstracts of grants concerned with specific research areas are sent on a regular basis, upon request, to NCI staff such as members of the Breast Cancer Task Force and the Laboratory of Toxicology.

This fiscal year, Toby Friedberg, a member of the Branch, again drafted the annual Report of the National Cancer Advisory Board. She attended meetings of the Board and contacted necessary staff members in order to draft this report, and is now gathering information for the 1981 report.

REVIEW AND REFERRAL BRANCH

Effective May 4, 1980, the Review and Referral Branch has been reorganized into a Grants Review Branch and a Contracts Review Branch, and future Annual Reports will reflect this change. However, because nearly all of the activity of the Branch for this reporting period is either completed or already under way, and because the acting Chief of the Grants Review and the Chief of the Contracts Review are the same, this report is presented as a single entity and the now outmoded name used for convenience. The Review and Referral Branch is responsible for (1) internal NCI program assignment of all grant applications referred to the Division of Cancer Research Resources and Centers (DCRRC); (2) assignment of grant applications for program project, core, construction, and other large instrument or special-purpose grant applications to appropriate NCI review committees; (3) scientific merit review of the applications noted under (2) above; (4) review of research contract proposals submitted in response to RFP's; and (5) preparation of summary reports of the recommendations and evaluations of each committee review and of each site visit. This involves formulating goals, criteria, and strategy to meet these goals, as well as managing the activity. The latter includes analyzing, evaluating, and reporting. The Branch also serves as liaison between the Division of Cancer Research Resources and Centers and the Division of Research Grants, NIH, in matters related to review and referral.

During the period of this report, the previously reported reorganization of the National Cancer Institute resulted in the transfer of six contract peer review committees and two grant application review committees to the Branch. In addition, the workload required the use of an ad hoc construction application review committee. Thus, the original three committees or subcommittees have grown to 11 chartered committees and one ad hoc committee. As in the past, there were also a number of special review committees or ad hoc reviews developed for one-time use to assure prevention of conflict-of-interest situations; e.g., when applications were received from review committee members, or in cases when none of the chartered committees had sufficient, appropriate expertise.

The Review and Referral Branch provides initial peer review for large-scale multidisciplinary research project (program project) applications intended to generate knowledge of cancer, its biology, or control. Each application is classified for review according to its major emphasis as either a clinical or basic science proposal. The Branch also provides initial peer review of proposals for indirect support of research at Cancer Research Centers and other organizations through core funding of shared resources and services. Such services might include computer use, biostatistics information, centralized tissue and cell-culture facilities, and electron microscope laboratories. During fiscal year 1980, five committees (or subcommittees) reviewed the diverse applications submitted. During the same period six contract review committees provided peer review and technical evaluation of research support proposals submitted in response to new RFP's or as renewals of contracts previously awarded. Balance and expertise in each committee's deliberations are assured by members who are active investigators, and are nationally and

internationally recognized leaders in many of the disciplines relevant to the cancer problem. The disciplinary composition of each committee is matched, insofar as possible, with the disciplinary composition of the applications it reviews. Committee recommendations regarding grants are considered by the National Cancer Advisory Board as required by the National Cancer Act.

The Grant Application Review Committees:

The Cancer Special Program Advisory Committee (CSPAC) reviews proposals requesting program project support or construction support for basic science. Review of these complex, multidisciplinary applications constitutes the bulk of the committee's work. CSPAC has 13 members with expertise in the basic sciences related to the cause, treatment, and prevention of cancer. Members must understand medical school and university organization, administration of program projects and construction projects, and be sensitive to the effect on the applicant institution caused by initiation, continuation, or termination of a large-scale project. The group advises the NCAB and the Director, NCI, regarding the merit and probable success of the basic research program projects that come before them.

The Clinical Cancer Program Project and Cancer Center Support Review Committee was established during 1978 by merging two previously independent committees in compliance with the objective of the Department to reduce the number of advisory committees. Through two independently functioning subcommittees, applications are reviewed for program project support concerned with clinical problems in cancer, in one case, and applications for core support of comprehensive, clinical, and specialized research centers in the other. Under normal workload conditions, both subcommittees review construction applications related to their activities. However, ad hoc construction review was utilized this year to relieve the workload of the subcommittee somewhat. Because of the complexity and volume of the work required, each subcommittee functions independently. The committee charter provides that each subcommittee consist of 20 members appointed by the Director of the NCI.

(A) The Cancer Center Support (Core) Review Subcommittee (CCS) provides merit review for requests to fund core grant applications submitted by designated comprehensive cancer centers and by specialized centers as well as applications to fund construction or renovation of related cancer facilities. The subcommittee is also a resource for advice on related cancer research programs, current status of ongoing centers, and identification of areas for future emphasis. Review by CCS helps alert the NCAB to the problems raised by, and the opportunities inherent in, the applications from the centers in terms of the mission of the NCI.

The responsibilities of the CCS require that the members of the committee have broad knowledge of the basic sciences that can contribute new information about the cause and prevention of cancer and of the clinical sciences involved in prevention, diagnosis, and treatment of cancer. In addition, knowledge of the administration and organization of medical schools, universities, and freestanding cancer research organizations is essential. Sensitivity to

institutions' organizational needs is important. Reviewers must be able to recognize those management practices that encourage good research.

(B) The Clinical Cancer Program Project Review Subcommittee (CCP) provides merit review of applications requesting support of clinical program projects and related cancer research programs. It also identifies areas for future emphasis, and makes suggestions for innovative approaches to the cancer problem. The review of large clinical research grant applications requires special expertise in cancer clinical trials; understanding of the special demands of research with human subjects, of hospital and medical school organization, of the administration of program projects; and, most importantly, detailed expert knowledge of the diagnosis and treatment of all types of cancer.

The Cancer Clinical Investigation Review Committee (CCI) was reassigned to the Branch during the summer of 1978. Its major function is to review applications in support of cooperative clinical trials and related areas of cancer research. The review of cooperative clinical trials requires that the reviewers be sensitive not only to the usual issues of scientific merit of clinical research, but to the special problems involved in cooperative research where the standardization and effective management of clinical research efforts at several institutions over wide geographic distances are also important factors. The review by this committee provides the NCAB and the Director, NCI, with information concerning the problems and opportunities regarding the testing of chemotherapeutic agents and multimodality approaches to therapy.

Cancer Control Grant Review Committee (CCG). This committee was assigned to the Branch in October 1978. Its function is to review control activity grant applications involving education in oncology, cancer epidemiology and statistics, rehabilitation research, regional programs in cancer control, and training of paramedical personnel in cancer detection techniques. The Committee advises the NCAB and the Director, NCI, on the scientific merit of these applications and identifies problems to be solved and opportunities which could be exploited.

In addition to the chartered committees, an ad hoc group for construction review was tried on an experimental basis for the final cycle of fiscal year 1978 because (a) of the heavy workload, and (b) it was thought that although construction applications should be viewed as closely allied to science, these applications are sufficiently different from other types to justify a separate review body. The experiment appears to have been successful in that no unusual problems manifested themselves during the initial review or the NCAB review during fiscal year 1979. A sufficient number of applications were involved to suggest a reliable trial. Therefore, this year the use of a similar group was continued and construction applications ordinarily assigned to other committees were assigned to it for review. This procedure is still considered exploratory, and the effects of reviewing construction applications by this means will be closely monitored by review and program staff, despite its apparent success.

The Contract Proposal Review Committees:

The review committees, having responsibility for review of research contract proposals (as distinguished from resource contract proposals) were assigned to this Branch on October 1, 1978. Previously, reviews of these proposals had been done primarily by chartered committees coordinated by program staff, many of whom served as executive secretaries on a part-time basis. Before these committees were assigned to this Branch, a number of them were consolidated from a few committees with generally similar activities into single committees (Biometry and Epidemiology, Cause and Prevention, Clinical Trials, and Tumor Immunology). This consolidation of committees was done by revision of their charters in furtherance of the Department's objective to reduce the numbers of advisory bodies being utilized.

Biometry and Epidemiology Contract Review Committee. This Committee advises the Director, NCI, as well as the Directors of the Division of Cancer Cause and Prevention and the Division of Cancer Research Resources and Centers on the technical merit of contract proposals responsive to RFP's relating to cancer epidemiology and biometry. Because of the nature of their studies, the intramural program staff uses such contracts to a large extent to ensure receiving sufficient data in useful forms for their research. Otherwise, the staff would not have available to it the data necessary to achieve its mission. Contracts are also used for the usual reasons by this staff. A large amount of this work is done collaboratively with extramural research institutions.

Cancer Control Intervention Programs Review Committee. This Committee advises the Director, NCI, and the Directors of the Division of Cancer Control and Rehabilitation and the Division of Cancer Research Resources and Centers on the technical merit of contract proposals in the fields of cancer prevention and detection, diagnosis, pretreatment evaluation, treatment, rehabilitation, and continuing care. Programs of a more applied nature than the research grant programs reviewed by the Cancer Control Grant Review Committee are stimulated and implemented through RFP's. The contract proposals received in response to such RFP's are reviewed by this Committee. Committee members must understand not only the underlying science and clinical medicine involved but the implications for cancer control of the activities which these programs support.

Cause and Prevention Scientific Review Committee. This Committee advises the Director, NCI, and the Directors of the Division of Cancer Cause and Prevention and the Division of Cancer Research Resources and Centers on the technical merit of contract proposals for research into chemical, physical, and viral carcinogenesis. There are a number of programs in the Division of Cancer Cause and Prevention which use such contracts in furtherance of their mission.

Clinical Trials Committee. This Committee advises the Director, NCI, as well as the Directors of the Division of Cancer Treatment and the Division of Cancer Research Resources and Centers on the scientific and technical merit of contract proposals involving clinical trials and related studies. The

Division of Cancer Treatment uses such contracts when it wishes to stimulate clinical trials in which it will exercise some control of the design, conduct, and statistical analysis of the research.

Developmental Therapeutics Committee. This Committee advises the Director, NCI, as well as the Directors of the Division of Cancer Treatment and the Division of Cancer Research Resources and Centers on the scientific merit of contract proposals for development of therapeutically useful anticancer agents through research in radiobiology, molecular biology, biochemistry, and pharmacology. In compliance with the Department's goal to reduce advisory bodies, the charter of this Committee will be allowed to lapse. The relatively small numbers of proposals which would be reviewed by it will be reviewed by other relevant committees or ad hoc groups in the future.

Tumor Immunology Committee. This Committee advises the Director, NCI, and the Directors of the Division of Cancer Biology and Diagnosis (DCBD), the Division of Cancer Research Resources and Centers, and the Division of Cancer Treatment on the scientific merit of contract proposals involving cancer immunobiology, immunodiagnosis, immunotherapy, and the immunologic aspects of cancer cause and prevention. As a result of the de-emphasis of the use of contracts for support of research by DCBD, the workload of this committee has been sharply reduced. Therefore, its charter will also be allowed to lapse and its work will be done by other relevant committees or ad hoc groups in the future.

Summary:

During the year, the Referral Office received and assigned approximately 3,423 applications. Of these, 121 were program projects.

The grants review activity of the Branch is shown in detail in Table I. The five chartered, ad hoc or special review grants committees or subcommittees of the Branch reviewed 477 grant applications requesting a total of $684,567,762. Sixty percent or 286 applications were recommended for approval with recommended budgets totalling $246,736,450 or 36 percent of the total requested in all of the applications reviewed. The recommended budgets amount to 44 percent of the total requested for all the applications approved. A total of $309,782,687 was disallowed in the approved grants. These data are provided in more detail in Table I. It should be noted that programmatic and financial considerations often dictate budget negotiations which further reduce the percentage paid to below the recommended level.

Table II gives details of the activities of the contracts review committees between the dates indicated. A total of 19 RFP's resulted in reviews of 283 proposals. In addition, 65 new and renewal proposals were reviewed. Financial data beyond the totals requested are not reported here because not all proposals recommended for approval are awarded and many of the awarded proposals are negotiated so that the financial information available to the Branch changes significantly.

It is of interest that the funding of the scientific evaluation grants awarded by NCI to support all the reviews reported totalled $1,140,000 in this fiscal year. This is 0.2 percent of the $684,567,762 requested, and 0.5 percent of the $556,519,137 approved.

The significance of the work of the Branch to the mission of the NCI is suggested by these figures. However, the true significance lies in the expert advice obtained which permits the National Cancer Advisory Board and the Director, NCI, to select for funding that research best suited to fulfill the mission of the NCI and the National Cancer Program.

TABLE I

GRANTS REVIEW ACTIVITY: OCTOBER 1, 1979 THROUGH SEPTEMBER 30, 1980

REVIEW GROUP*	DIRECT COSTS REQUESTED: ALL APPLICATIONS: NO.	AMOUNT	DIRECT COSTS RECOMMENDED: APPROVED APPLICATIONS: NO.	AMOUNT	DIRECT COSTS REQUESTED: APPROVED APPLICATIONS	% OF AMOUNT REQUESTED RECOMMENDED IN APPROVED APPLICATIONS	AMOUNT DISALLOWED ON APPROVED APPLICATIONS	APPROVAL RATE: NO.	APPROVAL RATE: AMOUNT
CAK	36	$ 85,800,716	32	$ 44,815,671	$ 82,540,632	54%	$ 37,724,961	89%	52%
CCP	29	138,983,327	26	43,717,933	131,850,252	33%	88,132,319	90%	31%
CCG	173	138,137,738	59	28,197,782	59,321,968	48%	31,124,186	34%	20%
CCS	26	132,391,826	22	56,118,681	129,235,799	43%	73,117,118	85%	42%
CCI	139	94,860,447	113	38,775,621	82,836,907	47%	44,061,286	81%	41%
SRC	65	83,027,492	27	27,783,248	60,013,712	46%	32,230,464	42%	33%
AD HOC CONST.	9	11,366,216	7	7,327,514	10,719,867	68%	3,392,353	78%	64%
TOTAL	477	$684,567,762	286	$246,736,450	$556,519,137	44%	$309,782,687	60%	36%

Total Direct Costs recommended $246,736,450 (36% of total requested).
Total of requested budgets of disapproved applications $128,048,625 (19%).
Total of requested budgets disapproved plus amounts disallowed on approved applications $437,831,312 (64%).

*CAK=CANCER SPECIAL PROGRAM ADVISORY COMMITTEE
CCP=CLINICAL CANCER PROGRAM PROJECT REVIEW COMMITTEE
CCG=CANCER CONTROL GRANT REVIEW COMMITTEE
CCS=CANCER CENTER SUPPORT GRANT REVIEW SUBCOMMITTEE
CCIRC=CANCER CLINICAL INVESTIGATION REVIEW COMMITTEE
SRC=SPECIAL REVIEW COMMITTEE
AD HOC CONST.=AD HOC CONSTRUCTION

In some instances Executive Secretaries conducted ad hoc reviews in which committee members were not involved. The totals for these meetings have been added to the totals for that Executive Secretary's committee activities.

TABLE II

CONTRACTS REVIEW ACTIVITY: OCT. 1, 1979 THROUGH SEPT. 30, 1980*

REVIEW GROUP**	# OF RFP's	# OF PROPOSALS IN RESPONSE TO THE RFPs	TOTAL AMOUNTS OF RFP PROPOSALS	NO. OF NEW AND RENEWAL PROPOSALS	TOTAL AMOUNTS: NEW & RENEWAL PROPOSALS	TOTAL # OF PROPOSALS	TOTAL AMOUNTS
CCIPRC	1	59	$ 9,600,000	7	$ 2,140,444	66	$11,740,444
TIC***	1	2	315,195	9	526,657	11	841,852
CPSRC	3	51	24,645,082	22	7,474,624	73	32,119,706
DTC	2	36	2,266,376	0	-0-	36	2,266,376
CTC***	5	131	12,754,483	4	1,930,737	135	14,685,220
BECRC***	7	7	890,782	23	8,281,606	30	9,172,388
TOTAL	19	286	$50,471,918	65	$20,354,068	351	$70,825,986

*As of the deadline for submitting this report, 2 RFP's and 26 new and renewal proposals are scheduled to be reviewed during the remainder of the reporting period.

**CCIPRC=CANCER CONTROL INTERVENTION PROGRAMS CONTRACT REVIEW COMMITTEE
TIC=TUMOR IMMUNOLOGY COMMITTEE
CPSRC=CAUSE AND PREVENTION SCIENTIFIC REVIEW COMMITTEE
DTC=DEVELOPMENTAL THERAPEUTICS COMMITTEE
CTC=CLINICAL TRIALS COMMITTEE
BECRC=BIOMETRY AND EPIDEMIOLOGY CONTRACT REVIEW COMMITTEE

***Amounts include ad hoc reviews conducted by the Committee's Executive Secretary, in which committee members were not involved.

COOPERATIVE MINORITY BIOMEDICAL PROGRAM

Since the Cooperative Minority Biomedical Program (CMBP) was formed in 1975, its participation in cancer research and training activities has increased significantly. Each year the Division of Cancer Research Resources and Centers staff has made consolidated efforts to broaden the scope of activities that would impact on the central thrusts of the National Cancer Program mission.

The CMBP operates through two Intra-agency Agreements: (1) between the National Cancer Institute (NCI) and the Division of Research Resources (DRR); and (2) between the NCI and the National Institute of General Medical Sciences (NIGMS). These agreements provide collaboration in the funding of grants in research, training, fellowships, visiting scientists, young investigator awards, and honors undergraduate research training awards and symposiums. The DRR goal is to provide support to strengthen the institutional health-related research capabilities of four-year colleges, universities, health professional schools, and other eligible institutions with significant enrollments of ethnic minority persons. The MARC goal is to foster research and research training in basic medical, biological, preclinical, clinical, and related natural and behavioral sciences. The uniqueness of the MARC program includes five-year institutional awards; all other awards range from one to three years.

To augment these activities, the National Cancer Institute provides funds and programmatic advice to support meritorious research and training that have an impact on the overall mission of the National Cancer Program in either the MBS or MARC programs.

All initial scientific merit reviews are conducted by the General Research Support Review Committee (GRSPB) for DRR grants, and the National Advisory General Medical Sciences Council of the NIGMS for the MARC grants. Program relevance determinations are made by the NCI Special Advisory Group for minority research and training activities and are approved by the National Cancer Advisory Board.

In fiscal year 1979, the NCI provided $1,581,000 to fund in whole or in part numerous applications in the MBS and MARC programs. In fiscal year 1980 the total amount awarded was $1,717,000. Although these awards are funded in part or in whole, they represent NCI's involvement with approximately 68 minority institutions.

The Grants Administration Branch (GAB) performs all business activities attendant to the administration of the NCI extramural grant program for research, centers, control, construction, training, and fellowships. It participates in a managerial capacity with the Directors of the various Divisions and their staff in the formulation and execution of extramural program plans. It interprets, applies, and participates in the formulation of policy affecting the management of grants, develops the Institute's position on extramural business management issues, provides financial and administrative review of grant applications and negotiates the amount of grant awards, and processes applications and all other documents related to extramural programs. This year, NCI will issue over 4000 award notices for a total of $514,670,000.

GAB is comprised of two sections in addition to the Office of the Chief, the Grants Management Section with a staff of 32 and the Processing Section with a staff of 22. In 1980, GAB continued with the goals established last year: equalization of grant workload; improving NCAB preparation; and improvement of resources.

1. Equalization of Grant Workload. GAB is continuing the efforts begun late in fiscal year 1978 to recycle grants out of the 4th quarter. The goal is to achieve a maximum of 25 percent funding in the final quarter. Because of late appropriations and late release of reserves, there will always be awards issued in the final month of the fiscal year. However, major steps are being taken to prevent an unbalanced workload caused by these factors. To spread the number of grants more equitably throughout the fiscal year, August and September type 1 awards for other than 12 months, are being negotiated by either short-funding (applications with poor priorities), or offering additional months of support (for applications with good priorities), so that their anniversary dates will no longer fall in the fourth quarter (July, August, September). In fiscal year 1978, GAB shifted 136 grants; in fiscal year 1979, 171; and in 1980, 106.

   In order to obligate as many dollars as possible before the fourth quarter, applicants are requested to submit all noncompeting, continuation (type 5) applications by April 1. This year GAB is concentrating on the large grant programs CORE (P30) and program projects (P01). In addition, May applications in the fundable range were distributed to the grants management specialists early for prenegotiation and collection of necessary documentation so that awards could be issued as soon as possible after the Board meeting. In fiscal year 1978, 49 percent of the grants were obligated in the fourth quarter. In fiscal year 1979, this figure had been reduced to 30 percent, and in fiscal year 1980 reduced further to 28 percent. GAB continues to encourage early development of funding plans and "pay lists" and the use of the "early award" authority.

2. Improving National Cancer Advisory Board Preparation. The major achievement in this area is the elimination of "Board books," the bound sets of summary statements prepared for each member at the Board meeting. This material has been reduced from 35 sets of 6 books, measuring 15 inches, to one set for the use of the Executive Secretary, plus a set of loose summaries, available for duplication purpose if necessary. Each Board member's books have been replaced by a folder of summaries received by NCI too late to mail and a folder containing only those summaries Board members have identified for individual discussion at the meeting. Elimination of the Board books represents a reduction in the amount of paper provided annually to Board members of 354,000 pages (45 yards of paper) weighing over 1-1/2 tons.

   As an informational aid to Board members, a three-part index of Initial Review Group recommendations is provided to each member at the meeting. This index presents one-line entries for each application, giving the initial review group recommendation of approval or disapproval, the priority score for approvals, the first year's recommended level, and the number of years recommended. The information is presented by grant number, by investigator, and by program/cancer activity.

   Late summary statements continue to be a problem. A control system has been instituted for the receipt of summary statements and to alert review and program staff of potential late summaries by distributing periodic lists of unreceived summaries.

3. Improvement of Resources.

   a. To supplement the NCI Policy Manual instituted last year, a procedural manual is being developed for GAB staff to insure compliance with the requirements of the policies.

   b. The Branch conducted a thorough study of the various functions involved in preparing for the Board meetings, and presented for consideration several proposals to improve Board preparation and presentation. It covered such functions as monitoring the receipt and distribution of both applications and summary statements, program director responsibility for each application, assembling of material for both staff and Board members, identification and resolution of problem areas such as late summary statements and printing difficulties, and presentation of review material at the meeting. As a result of this study, an NCAB operations manual will be developed incorporating those recommendations which have been accepted and which are being implemented.

Site visits. This year, GAB began stressing the advantages of site visits as a management tool. The specialists are encouraged to visit those institutions especially that appear to have less than average expertise in the administration of grants. By making on-site visits, staff is able to review the quality of grants management and to resolve ongoing problems and, at the same time help them improve the overall quality of grants management for their institutions.

GRANTS FINANCIAL AND DATA ANALYSIS BRANCH

The Grants Financial and Data Analysis Branch is responsible for fund control, maintaining financial data, providing information to requestors inside and out of NIH, and for analysis of financial data necessary to provide funding guideline recommendations, budget preparation, and advice for grants financial policy decisions.

Computer specialists in the branch have written computer programs which have automated work previously done manually and have assisted in special projects to help handle the increasing workload more effectively. They are responsible for creating and maintaining computer programs for the Grants Financial and Data Analysis Branch and for providing programming assistance to the Grants Administration Branch, Research Analysis and Evaluation Branch, and Review and Referral Branch.

To provide fund control for NCI grants, the GFDAB maintains an accounting data set which lists all grants selected for funding as well as all applications recommended for approval in a given fiscal year. Information necessary to identify a grant, funding codes, financial information such as award amounts, and the scientific codes used in budgeting and fund control are maintained on this data set. Computer queries sort the data in many ways to reconcile NCI's totals with the Division of Financial Management, NIH; to indicate the status of funds by mechanism, Division, and research program; and to produce reports for financial plans, variance reports, and deficiency reports for the Office of Financial Management. To reduce errors and save clerical time in the preparation of award statements, common account numbers and Program Directors' names have been computerized in fiscal year 1980 for ongoing traditional R01 grants using reconciled data from fiscal year 1979. It should be possible to computerize these codes for other grant programs in fiscal year 1981. Through daily updating of award information, it is possible to determine the status of actual obligations at any given time. Use of computer programs makes it possible to estimate commitments not yet awarded. Both types of information are used in most financial reports.

As a result of the reorganization of NCI, a Division code is entered for each grant in order to identify actual and potential expenditures. This enables staff to sort grants by NCI program, mechanism, cancer activity and Division. This information is used for funding guideline recommendations and program reviews. To further simplify data processing and promote efficiency, the development of a master file to provide a single data base for grants financial information was undertaken in fiscal year 1979. The master file contains expanded information about funded grants and unfunded approvals included on the fiscal year data set. It also includes amounts committed for future years, which are used in budgeting. Use of the master file expedites updating of award data by linking directly to the NIH Division of Financial Management system, and

provides a better means of checking the accuracy of data. Plans exist for expansion of the master file during fiscal year 1981 to include current data on competing applications which are now maintained on several data sets. This will simplify production of such pre-award listings as ranking lists and maintenance of tables of competing applications. The master file's contributions this year have been generation of data sets for fund control, historical information, and tables used in preparing special reports.

To improve fund control and budgeting for the DCRRC Review and Approval in-house budget and Division of Cancer Control and Rehabilitation (DCCR) grants, codes were developed and entered in appropriate data sets during fiscal year 1980. A data set which summarizes monthly obligations by sub-object class and for individual conferences, research and development contracts, and interagency agreements was developed for Review and Approval fund control. This data set can be sorted in a variety of ways using programs in order to project and account for quarterly and monthly expenditures. During fiscal year 1979, the need for more detailed information on cancer control R18 grants became apparent. In fiscal year 1980, DCCR Program Directors were asked to identify all ongoing grants and approved applications according to three budget categories--control, rehabilitation research, and centers outreach--which correspond to the grant common account numbers. Two further categories within control--prevention and other centers--were identified for DCCR use. In future years, only new approvals will need to be coded.

The GFDAB provides data and suggests funding options to aid in developing funding guidelines for NCI grant programs. The GFDAB is responsible for insuring communication on grant funding decisions between the Divisions and the Director, NCI, and to facilitate and expedite the process by making fiscal recommendations and by providing concise program information to each Division Director and Program Director. For each round of applications, detailed lists of recommended applications arranged in priority-score order by cancer activity and with individual and cumulative costs are distributed to Division and Program Directors. A form which summarizes recommended applications by cancer activity and provides a space for funding plan recommendations, including priority-score cutoffs and exceptions, plus any other appropriate tables are included in a package with the detailed lists. Division Directors' recommendations are consolidated by the GFDAB for discussion at a Division Directors' funding plan meeting. The Directors' decisions are summarized in a memorandum, distributed to staff, and recorded on the fiscal year data set for fund control.

Budget preparation continues to be a major responsibility of the GFDAB. The Branch works with the Financial Manager's Office to allocate funds by grant mechanism and to advise of reasonable budget requests for grant programs. In fiscal year 1980, in response to a request from several sources, a paper was written detailing how requested, approved, and awarded amounts are projected for various grant programs. Briefly, using

current data on commitments and assumptions based on historical trends, as well as knowledge about specific grants and programs, the financial analysts develop requirements and funding projections for each year in each budget submission. The detailed data showing numbers and dollars for grants by Division, mechanism, type, program, thrust, and cancer activity are entered into a budget data base.

A series of computer programs run as a package against this data base produces all the crosswalk tables now required for a budget submission. The computer programs have increased the accuracy of a budget submission and reduced the paperwork and clerical time enormously. Without them it would be a leviathan task to produce the complex set of budget tables required. The automation of the system has the additional benefit of providing time for data analysis and permitting presentation of budget data in virtually any format desired. It has become a simpler task to provide each Division with data relevant to its programs and to produce a consolidated budget for all grant programs. Modifications are made as required. Throughout the course of a fiscal year, the GFDAB answers questions from the Financial Manager's Office about the various budget submissions regarding items such as funds required to pay to certain priority scores or certain percents of requirements, how additional funds would affect funding, the effects of increased or decreased funds on future years, and the impact of various funding policies.

Program reviews were instituted in fiscal year 1979 by the Director, NCI. In these reviews, the Director discusses the funding status of grant and contract programs with each Division Director to determine the need for transferring funds from one area to another. The GFDAB provides charts and tables showing the status of grant funds in terms of commitments and requirements. In fiscal year 1980 the grants data were added to the budget data base. Computer programs were written to produce the necessary tables and to allow the capability for more timely responses to additional questions regarding the grants data for the program reviews. An additional advantage of having the data in the same format as the budget data is that the budget programs can be run against these data for comparison and backup.

In addition to providing advice and answering questions about grant funds and budget, the GFDAB serves as a source of current and historical information on nonscientific aspects of cancer grants for NCI staff, the Budget Office, Program and Management Staff, the Directors of NCI and DCRRC, Congress, the National Cancer Advisory Board, and the public. Monthly lists of active grants are provided to Program Directors, the Director, DCRRC, and other NCI staff. Typical requests are for lists of unfunded grants; summaries of applications showing requested funding, amount recommended for award, and amounts awarded in a given fiscal year; and lists or summaries of grants awarded to specific states, institutions, or principal investigators. The GFDAB responds to the cancer grants portion of the Congressional Questions for the Director, NCI, for each Congressional Budget Submission.

Historical information on each grant program is available on individual data sets featuring detailed lists of grants and competing applications and summary tables for each fiscal year back to 1970. These data are used for budget projections and to provide historical summaries of fiscal information. To facilitate and expedite accurate responses to special requests or analyses involving historical data for both applications and awards, comprehensive history data sets for each fiscal year between 1970 and 1980 were created in fiscal year 1980. These data sets contain applications for each grant program taken from the IMPAC system and awards reconciled with DFM taken from the GFDAB system. This assures that award information will be accurate and consistent with past reports and tables. Codes such as those for cancer activity and mechanism were made consistent with fiscal year 1980 codes so that the data sets will be compatible with computer programs now in use and comprehensible to the current user.

The GFDAB distributes several booklets each year in addition to budgets, program reviews, special reports, and monthly active listings. Several times a year a booklet, NCI Grant Programs Status of Funds is printed and distributed to NCI staff and NCAB members. Books listing grant awards by principal investigator and by state and institution are printed and distributed to NCI staff each fiscal year.

In order to consolidate historical data on cancer grants, Grants Financial Data, a compendium of tables and charts summarizing data from 1970 to present is updated annually. Summary tables of requested, recommended, awarded, and unfunded amounts for each grant program are reprinted from individual data sets. Additional tables show grants by categories such as research, manpower, and total grants. Other tables show awards by research thrust, cancer activity, NCI program, budget category, type of institution, and state and institution. For Manpower Programs, tables show number of trainees and categorize trainees by academic or professional degree. Lists of awards for the current fiscal year are provided for programs with relatively small numbers of grants. Additional tables are added or deleted as appropriate each fiscal year. For example, in fiscal year 1979, tables summarizing direct, indirect, and total award costs by mechanism from fiscal year 1970 through 1979 were added. In short the Grants Financial Data provides a central source of historical data on cancer grants, and an overview of how grant dollars are spent, trends in grant applications and awards, and the current status of grant programs as indicated by numbers of applications and awards, percents funded, geographic distribution of awards, and types of research being funded.

The GFDAB was involved in several major special projects in fiscal year 1980. The GFDAB provided tables to support a recommendation that the authority of the Director, NCI to make early awards without NCAB approval be increased from $35,000 to $50,000. The tables provided a comparison by fiscal year from 1972 through 1979 of the number of new traditional R01 grant awards less than $35,000 to those less than $50,000. To

provide an additional perspective on the relative value of the awards from 1972 to 1979, average award amounts for each year were adjusted using the Biomedical R&D deflator with 1972 as the base year. Another project was inspired by level or minimally increasing budgets and steadily increasing inflation which have produced greater competition between traditional R01 grants and program projects (P01's) for research grant funds. A paper presented to the Executive Committee, NCI for discussion and eventually policy decisions and action, outlines various issues critical to program projects such as budgeting, allocation of funds, the funding selection process, the quality of P01's, and scientific review.

The need to develop various approaches to tightening budgets and increasing inflation resulted in the expansion in fiscal year 1980 of two projects initially done in fiscal year 1979. The CFDAB was asked by the NCAB to make a detailed study of the impact of three-year versus five-year awards in specified grant programs, the traditional program, program projects, centers, and clinical cooperative groups. It was found that in programs involving large grants with high renewal rates and implied long-term commitments, such as program projects, centers, and clinical cooperative groups, five-year awards are more cost efficient for NCI and generally more satisfactory to the grantee because of increased stability and reduced paperwork.

In response to NIH efforts to stabilize the science-base activities in the budget, the CFDAB projected trends for Research Project Grants (R01, P01, and R23) for fiscal years 1980-1984 for four funding alternatives, maintaining a constant number of grants, funding through a designated priority score, being held to a level budget, and maintaining a constant number of competing grants. To provide a backdrop, historical data were provided for fiscal years 1970-1979 and projected budgets were used for 1980 and 1981. Tables were prepared showing the numbers of awards, annual budget increases, priorities funded, percentage of grants funded, and amounts of unfunded approvals.

BUDGET DISTRIBUTION

FISCAL YEAR 1980
(Dollars in Thousands)

PROGRAM	$	$	$
Research			
Traditional Program		$200,171	
New Investigator Research Awards		3,418	
Conference Grants		922	
Scientific Evaluation		1,900	
Program Projects		100,447	
Organ Site Program			
Bladder	$5,039		
Large Bowel	5,692		
Prostate	4,730		
Pancreas	1,800		
Subtotal		17,261	
Creg			
DCCP	2,258		
DCT	4,502		
Subtotal		6,760	
Clinical Cooperatives		35,534	
Subtotal Research			$366,413
Resource Development			
Centers			
Cancer Center Support Grants	66,435		
Exploratory Projects	200		
Subtotal		66,635	
Clinical Education		10,904	
Careers			
RCA	163		
RCDA	4,120		
Subtotal		4,283	
National Research Service Awards			
Individual Fellowships	4,213		
Institutional Awards	22,901		
Subtotal		27,114	
Construction		11,000	
Subtotal Resource Development			119,936
Cancer Control			
Cancer Control Grants		25,715	
Centralized Cancer Patient Data System		2,606	
Subtotal Cancer Control			28,321
TOTAL			$514,670

DISTRIBUTION OF AWARDS

FISCAL YEAR 1980
(Dollars in Thousands)

	REQUESTED		RECOMMENDED		AWARDED		UNFUNDED	
	NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
Non-Competing Continuations	2535	$339,019	2535	$339,019	2535	$339,019	0	$ 0
Competing Renewals	910	220,073	813	140,124	464	93,179	349	46,945
New	2827	319,882	1934	171,455	617	65,497	1317	105,958
Administrative Supplements	(142)	14,760	(142)	14,760	(142)	14,760	(0)	(0)
Competing Supplements	90	7,269	69	4,491	39	2,215	30	2,276
TOTALS	6362	$901,003	5351	$669,849	3655	$514,670	1696	$155,179

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